(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
6 October 2005 (06.10.2005)

PCT

(10) International Publication Number
WO 2005/092918 A2

(51) International Patent Classification[7]: C07K 14/31, A61K 39/085, 48/00, C12N 15/62, C07K 19/00, C12N 5/06, 7/01

(21) International Application Number: PCT/GB2005/001084

(22) International Filing Date: 22 March 2005 (22.03.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0406408.5 22 March 2004 (22.03.2004) GB
0412419.4 3 June 2004 (03.06.2004) GB

(71) Applicant (*for all designated States except US*): UNIVERSITY COLLEGE LONDON [GB/GB]; Gower Street, London WC1E 9BT (GB).

(72) Inventors; and
(75) Inventors/Applicants (*for US only*): CHAIN, Benjamin, Michael [GB/GB]; 46 Cleveland Street, London W1T 4JF (GB). NAIR, Sean, Paddy [GB/GB]; 256 Grays Inn Road, London, WC1X 8LD (GB).

(74) Agent: WOODS, Geoffrey, Corlett; J.A. Kemp & Co., 14 South Square, Gray's Inn, London WC1R 5JJ (GB).

(81) Designated States (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) **Title:** TARGETING POLYPEPTIDE

(57) **Abstract:** A targeting polypeptide is provided that may be used to target a chosen antigen to an antigen presenting cell. Complexes comprising such targeting polypeptide and antigen, nucleic acids and vectors encoding them, and cells comprising the nucleic acids and vectors may be used in methods of immunisation and enhance the immunogenicity of the antigen.

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TARGETING POLYPEPTIDE

Field of the Invention

The present invention relates to targeting polypeptides and their use in targeting antigens to antigen presenting cells (APCs).

Background of the Invention

Staphylococcus aureus is a major causative agent of community and hospital acquired infections worldwide. The organism is an important pathogen due to a combination of invasiveness, toxin production, and antibiotic resistance. *S. aureus* causes a wide variety of clinical syndromes, ranging from uncomplicated infections of the skin to life-threatening toxic shock syndrome (TSS). The bacterium causes disease by producing large numbers of exoproteins or virulence factors. Among the many known virulence factors are two families of staphylococcal pyrogenic superantigens, staphylococcal enterotoxins (SEs) and toxic shock syndrome toxin-1 (TSST-1).

Superantigens bind to major histocompatibility complex (MHC) class-II on antigen presenting cells (B cells, monocytes, and dendritic cells) outside the classical antigen-binding groove, and activate T cells by binding with the variable region of the β chain of T cell receptors (Vβ-TCR). This cross-linking triggers the non-specific activation and proliferation of T cells, induces the production of high levels of a variety of cytokines, and causes toxic shock syndrome characterized by fever, rash, hypotension and multiple organ failure. Staphylococcal enterotoxins are responsible for many cases of food poisoning (intoxication) associated with ingestion of toxin-contaminated food. To date, more than thirteen staphylococcal enterotoxins have been described.

As well as these classical superantigens, *S. aureus* also produces a family of proteins that have sequence homology to the superantigens, these proteins are known as the staphylococcal exotoxin-like proteins (SETs) and are a family of polymorphic paralogs. They were first identified as a genetic locus encoding at least five exotoxin-like proteins (SET1-5). More recently, data from the sequencing of the genomes of several different *S. aureus* strains has revealed a large number of related (36-67%) *set* genes clustered on a genomic island. This putative pathogenicity island, which is present in all strains of *S. aureus* examined to date, codes for between seven and fourteen *set* genes, which have varying degrees of sequence homology. In addition,

there appears to be extensive inter-strain allelic polymorphism for each of the *set* genes. The International Nomenclature Committee for Staphylococcal Superantigen Nomenclature (INCSS) has recently recommended that the SETs be renamed staphylococcal superantigen-like exoproteins (SSLs) and numbered from SSL1 to SSL14 in clockwise order from the replication origin of the chromosome based on homology to the full complement of genes found in strain MW2. This nomenclature is essentially as described by Fitzgerald *et al* (*Infect. Immun., 2003,* **71**, 2827-2838) except that the numbering of the genes is in the opposite direction. To differentiate between allelic-variants the *ssl* gene is prefixed by the strain name.

The three-dimensional structure of one member of the family, SSL5 (previously SET3) has been determined. The crystal structure of this protein shows many of the characteristic structures of the superantigen superfamily, but significant differences also exist. In addition, SSLs do not show the main properties of classical superantigens, such as polyclonal T cell activation, pyrogenicity, or enhancement of endotoxin shock . The function of SSLs is therefore unknown.

Summary of the Invention

The present invention is based on the finding that Staphyloccal superantigen-like exoproteins (SSLs) are able to target themselves to antigen presenting cells (APCs). This targeting to antigen presenting cells and hence the antigen presentation pathway of these cells means that a chosen antigen can also be targeted to the antigen presenting cell facilitating presentation of the antigen and hence increasing immunogenicity. The invention may also be used to target antigens to antigen presenting cells in order to induce tolerance.

Accordingly, the invention provides for the use of a complex comprising:

(a) a targeting polypeptide comprising a staphylococcal superantigen-like protein (SSL), a fragment thereof or a variant of either, where the SSL, fragment or variant has the ability to target the complex to an antigen presenting cell; and

(b) an antigen and/or a nucleic acid molecule encoding an antigen,

in the manufacture of a medicament for use in immunization or the induction of tolerance.

The invention also provides a complex comprising:

(i) a targeting polypeptide as defined in any one of the preceding claims; and

(ii) an antigen or a nucleic acid encoding an antigen, wherein the antigen or encoded antigen is selected from a pathogenic antigen, auto-antigen, an allergen and a cancer antigen.

The invention also provides a virus comprising a targeting polypeptide of the invention

In addition, the invention provides:

- a nucleic acid molecule comprising a polynucleotide sequence encoding a targeting polypeptide and an antigen selected from a pathogenic antigen, auto-antigen, an allergen and a cancer antigen;
- a vector comprising a nucleic acid of the invention; and
- a cell comprising a nucleic acid or a vector of the invention or infected with a virus of the invention.

The invention also provides a method of loading antigen presenting cells comprising contacting an antigen presenting cell with a complex or virus of the invention. An antigen presenting cell which has been loaded with a complex or virus is also provided.

The invention additionally provides:

- a pharmaceutical composition comprising a complex of the invention, a nucleic acid encoding a targeting polypeptide and antigen of a complex of the invention, a vector comprising such a nucleic acid, a cell comprising such a nucleic acid or vector, a virus of the invention or an antigen presenting cell of the invention and a pharmaceutically acceptable carrier or diluent;
- a vaccine comprising a complex of the invention, a nucleic acid encoding the targeting polypeptide and antigen of a complex of the invention, a vector comprising such a nucleic acid, a cell comprising such a nucleic acid or vector, a virus of the invention or an antigen presenting cell of the invention; and
- a complex of the invention, a nucleic acid encoding a targeting polypeptide and antigen of a complex of the invention, a vector comprising such a nucleic acid, a cell comprising such a nucleic acid or vector, a virus of the invention, or an antigen presenting cell of the invention for use in a method of treatment of the human or animal body by therapy.

The invention also provides for the use of a nucleic acid encoding a targeting polypeptide and antigen of a complex of the invention, a vector comprising such a nucleic acid, a cell comprising such a nucleic acid or vector, a virus of the invention

or an antigen presenting cell of the invention in the manufacture of a medicament for use in immunisation.

The invention further provides a method of immunising a subject, the method comprising administering an effective amount of a complex of the invention, a nucleic acid encoding a targeting polypeptide and antigen of a complex of the invention, a vector comprising such a nucleic acid, a cell comprising such a nucleic acid or vector, a virus of the invention or an antigen presenting cell of the invention to a subject.

The invention also provides an agent for immunising a subject, the agent comprising a complex of the invention, a nucleic acid encoding a targeting polypeptide and antigen of a complex of the invention, a vector comprising such a nucleic acid, a cell comprising such a nucleic acid or vector, a virus of the invention or an antigen presenting cell of the invention.

Brief Description of the Figures

Figure 1 - Panel (a) shows the structure of SSL7, shaded from white (N-terminal) to dark (C-terminal). Panel (b) shows the structure of SSL7 (dark) optimally superposed on that of SSL5 (grey) and the same structure is shown on the right rotated by 90°. Panel (c) shows the structure of SSL7 (dark) optimally superposed on that of SPEC (grey) and the same structure is shown on the right rotated by 90°. Panel (d) shows the SSL7 dimer.

Figure 2 - shows residues in the SSL7 dimer interface with residue numbers being given on the x-axis, and buried surface area ($Å^2$) on the y-axis. The two forms are show by broken and unbroken lines.

Figure 3 – Panel (a) shows the results of FACS analysis of PBMCs (peripheral blood mononuclear cells) incubated with varying concentrations of SSL-7-FITC at 4°C and 37°C. The graph is representative of ten separate experiments carried out with PBMCs from healthy donors. Panel (b) shows the results of competition experiments between SSL9-FITC (top) and SSL7-FITC (bottom) with various molecules for binding to PBMCs. Results shown are from one representative experiment of three.

Figure 4 – shows the results of FACS analysis of PBMC stained with SSL7 (top) or SSL9 (bottom) and various markers. The results shown are representative of five separate experiments.

Figure 5 – shows the results of FACS analysis of PBMC-derived dendritic cells stained with SSL9, SSL7 or no stain. The results are representative of a set of three separate experiments on cells from healthy donors.

Figure 6 – shows that SSL and SSL9 interact selectively with dendritic cells. FACS results for unpurified Dendritic cells incubated with SSL7-FITC or SSL9-FITC and then stained for CD1a are shown. The numbers show the percentage of SSL positive cells that were also CD1a positive.

Figure 7 – shows that SSLs do not alter Dendritic cell morphology or cell surface phenotype. Panel (A) shows the morphology of Dendritic cells treated with SSL proteins. Results for lipopolysaccharide (LPS) and peptidoglycan (PG) are shown as positive controls. Results are representative of three experiments. Panel (B) shows FACS results for phenotypic analysis of dendritic cells treated with SSL proteins. Data are shown for expression of cell surface molecules on Dendritic cells that have been treated with SSL7 or SSL9. LPS and PG were used as positive controls. Expression of the indicated markers is shown by the solid histograms, whereas cells stained with relevant control mAb are indicated by the open line histograms. The numbers on each histogram correspond to the median fluorescence intensity (MFI) of mAb staining. Results shown are from one donor and are representative of similar data obtained from experiments carried out with dendritic cells from four different donors.

Figure 8 – shows endocytosis of FITC-Dextran by Dendritic cells exposed to SSL proteins. The results of one of three separate experiments are shown.

Figure 9 – shows that the effect of SSL protein on the T cell stimulatory capacity of dendritic cells. Panel (A) shows the effect of SSL7 (black bars) or SSL9 (empty bars) or medium alone (grey bars) on stimulation of autologous T cells in the presence or absence (M) of purified protein derivative (PPD). Data shown are mean ± SEM of 3 experiments.

Figure 10 – shows autologous T cell responses to Dendritic cells loaded with SSL7 or SSL9 protein. Data are mean ± SD of triplicate cultures from individual experiments.

Figure 11 – shows the effects of SSL protein on cytokine production. Purified protein derivative is used as control.

Figure 12 – shows antibody responses in human sera. Panel (A) show levels of SSL7 or SSL9 measured by ELISA. Results for a polyclonal rabbit antibody raised

against purified His-tagged SSL7 are included as a positive control. Data are representative of 3 experiments. Panels (B) and (C) show the results of a competitive ELISA with plates coated with either SSL7 (B) or SSL9 (C) where serum diluted 1:2000 (final dilution) was mixed with varying concentrations of SSL7, SSL9 or Emblp32 as indicated.

Brief Description of the Sequences

SEQ ID No: 1 provides the nucleotide sequence of a genomic fragment comprising the pathogenicity island SaPIn2 from *S. aureus* strain N315 which includes the *ssl1 to ssl5* and *ssl7 to ssl11* genes.

SEQ ID Nos: 2 to 11 provide the amino acid sequences of SSL1 to SSL7 and SSL7 to SSL 11 from *S. aureus* strain N315 and also indicate the location of the CDS of the genes in SEQ ID No:1.

SEQ ID No: 12 provides the nucleotide sequence of a genomic fragment from *S. aureus* strain N315, which includes the *ssl12 to ssl14* genes. The sequence indicated is the complement of the coding strand. The order of the genes in the indicated sequence going from 5' to 3' is *ssl14, ssl 13* and *ssl*12. The complementary sequence is given by SEQ ID No:103.

SEQ ID Nos: 13 to 15 provide the amino acid sequences of SSL14, SSL 13 and SSL12 respectively from *S. aureus* strain N315 and also indicate the location of the CDS of the genes in SEQ ID No:12. The start of each coding sequence indicated is the higher nucleotide position listed.

SEQ ID No: 16 provides the nucleotide sequence of a genomic fragment comprising the pathogenicity island SaPIn2 from *S. aureus* strain Mu50, which includes the *ssl1 to 3, ssl5* and *ssl7* to *ssl11* genes.

SEQ ID Nos: 17 to 25 provide the amino acid sequences of SSL1 to SSL3, SSL5 and SSL 7 to 11 respectively from *S. aureus* strain Mu50 and also indicate the location of the CDS of the genes in SEQ ID No: 16.

SEQ ID Nos: 26 to 36 provide the amino acid sequences of SSL1 to SSL11 respectively from *S. aureus* strain MW2 and also indicate the location of the CDS in SEQ ID No: 103.

SEQ ID No: 37 provides the nucleotide sequence of a genomic fragment from *S. aureus* strain NCTC8325, and includes the sequences of the *ssl1* to *ssl11* genes. The sequence indicated is the complement of the coding strand. The order of the

genes in the indicated sequence going from 5' to 3' is *ssl11 to ssl1*. The complementary DNA sequence is given by SEQ ID No: 104.

SEQ ID Nos: 38 to 48 provide the amino acid sequences of SSL1 to 11 respectively from *S. aureus* strain NCTC8325 and also indicate the location of the CDS of the genes in SEQ ID No:37. The start of each coding sequence indicated is the higher nucleotide position listed.

SEQ ID No: 49 provides the nucleotide sequence of a genomic fragment from *S. aureus* strain NCTC8325, and includes the sequences of the *ssl12 to ssl14* genes.

SEQ ID Nos: 50 to 52 provide the amino acid sequences of SSL12 to 14 respectively from *S. aureus* strain NCTC8325 and also indicate the location of the CDS of the genes in SEQ ID No:49.

SEQ ID No: 53 provides the nucleotide sequence of a genomic fragment from *S. aureus* strain EMRSA 16(252), which includes the sequences of the *ssl1* to *ssl5, ssl7, ssl9 to ssl11* genes. The sequence indicated is the complement of the coding strand. The order of the genes in the indicated sequence going from 5' to 3' is *ssl11 to ssl9, ssl7 and ssl5 to ssl1*. The complementary DNA sequence is given by SEQ ID No:105.

SEQ ID Nos: 54 to 62 provide the amino acid sequences of SSL1 to SSL5, SSL7, SSL9 to SSL11 respectively from *S. aureus* strain EMRSA 16(252) and also indicate the location of the CDS of the genes in SEQ ID No:53. The start of each coding sequence indicated is the higher nucleotide position listed.

SEQ ID No: 63 provides the nucleotide sequence of a genomic fragment from *S. aureus* strain EMRSA 16(252) and includes the sequences of the *ssl12 to 14* genes. The sequence indicated is the complement of the coding strand. The order of the genes in the indicated sequence going from 5' to 3' is *ssl14 to ssl12*. The complementary sequence is given by SEQ ID No:106.

SEQ ID No: 64 to 66 provide the amino acid sequences of SSL12 to 14 respectively from *S. aureus* strain EMRSA 16(252) and also indicate the location of the CDS of the genes in SEQ ID No:63. The start of each coding sequence indicated is the higher nucleotide position listed.

SEQ ID No: 67 provides the nucleotide sequence of a genomic fragment from *S. aureus* strain MSSA-476 which includes the *ssl11* to *ssl11* genes.

SEQ ID No: 68 to 78 provide amino acid sequences of SSL1 to SSL11 respectively from *S. aureus* strain MSSA-476 and also indicate the location of the

CDS of the genes in SEQ ID No:67.

SEQ ID No: 79 provides the nucleotide sequence of a genomic fragment from *S. aureus* strain MSSA-476 which includes the sequences of the *ssl12* to *ssl14* genes.

SEQ ID No: 80 to 82 provides the amino acid sequences of SSL12 to SSL 14 from *S. aureus* strain MSSA-476 and also indicate the location of the CDS of the genes in SEQ ID No:79.

SEQ ID Nos: 83 and 84 provide the nucleotide and amino acid sequences respectively of *ssl11* from *S. aureus* strain COL.

SEQ ID Nos: 85 and 86 provide the nucleotide and amino acid sequences respectively of *ssl12* from *S. aureus* strain COL.

SEQ ID Nos: 87 and 88 provide the nucleotide and amino acid sequences respectively of *ssl13* from *S. aureus* strain COL.

SEQ ID Nos: 89 and 90 provide the nucleotide and amino acid sequences respectively of *ssl14* from *S. aureus* strain COL.

SEQ ID Nos: 91 and 92 provide the nucleotide and amino acid sequences respectively of *ssl9* from *S. aureus* strain COL.

SEQ ID Nos: 93 and 94 provide the nucleotide and amino acid sequences respectively of *ssl10* from *S. aureus* strain COL.

SEQ ID Nos: 95 and 96 provide the nucleotide and amino acid sequences respectively of *ssl11* from *S. aureus* strain COL.

SEQ ID Nos: 97 and 98 provide the nucleotide and amino acid sequences respectively of *ssl12* from *S. aureus* strain COL.

SEQ ID Nos: 99 and 100 provide the nucleotide and amino acid sequences respectively of *ssl13* from *S. aureus* strain COL.

SEQ ID Nos: 101 and 102 provide the nucleotide and amino acid sequences respectively of *ssl14* from *S. aureus* strain COL.

SEQ ID No: 103 provides the complementary sequence to SEQ ID No: 12.

SEQ ID No: 104 provides the complementary sequence to SEQ ID No: 37.

SEQ ID No: 105 provides the complementary sequence to SEQ ID No: 53.

SEQ ID No: 106 provides the complementary sequence to SEQ ID No: 63.

SEQ ID No: 107 provides the nucleotide sequence of a genomic fragment from *S.aureus* strain MW2 which includes the *ssl1* to *ssl11* genes. The amino acid sequences of the encoded proteins are provided by SEQ ID Nos: 26 to 36 which indicate the position of the coding sequences in SEQ ID NO: 107.

Detailed Description of the invention

Throughout the present specification and the accompanying claims the words "comprise" and "include" and variations such as "comprises", "comprising", "includes" and "including" are to be interpreted inclusively. That is, these words are intended to convey the possible inclusion of other elements or integers not specifically recited, where the context allows. In some cases, where specific constituents are recited, the embodiment may, for example, consist essentially of such constituents.

The present invention is based on the finding that SSLs are able to target themselves to antigen presenting cells (APCs). The targeting to antigen presenting cells leads to the SSLs entering the antigen presenting pathway of the antigen presenting cells and being presented on the surface of the antigen presenting cells. This enhances the immunogenicity of the SSLs. The invention uses targeting polypeptides employing, or based on, the sequence of SSLs to target a chosen antigen to antigen presenting cells to enhance the immunogenicity of the chosen antigen. In effect, the targeting polypeptides are used to deliver a chosen antigen to an antigen presenting cell.

In some instances the targeting polypeptides are used to deliver a nucleic acid molecule encoding the antigen, rather than the antigen itself. The nucleic acid molecule will then give rise to expression of the antigen in the antigen presenting cell and the subsequent presentation of the antigen.

The invention employs targeting polypeptides comprising the polypeptide sequence of an SSL, a fragment of an SSL, or a variant sequence based on either, to target a chosen antigen or encoding nucleic acid to an APC. The invention uses complexes comprising the targeting polypeptide and antigen or an encoding nucleic acid to achieve delivery of the chosen antigen to an antigen presenting cell.

Targeting polypeptides

The targeting polypeptides employed comprise a staphylococcal superantigen-like protein (SSL), a fragment thereof or a variant of either, where the SSL, fragment or variant has the ability to target the targeting polypeptide to an antigen presenting cell (APC). The ability to target a polypeptide to an antigen presenting cell is referred to herein as targeting activity.

The targeting polypeptide may comprise the sequence of any naturally occurring SSL polypeptide. Such polypeptides may typically be isolated from *Staphylococcus aureus*.

The amino acid sequences of SSLs 1 to 14 from a variety of strains of *Staphylococcus aureus* are provided herein and any of these sequences may be present in a targeting polypeptide of the invention. The Table below indicates the corresponding SEQ ID Nos for the SSLs.

Table – SSLs

	***Staphylococcus aureus* strain and SEQ ID No for SSL**						
SSL	N315	Mu50	MW2	NCTC 8325	EMRSA 16(252)	MSSA 476	COL
1	2	17	26	38	54	68	84
2	3	18	27	39	55	69	86
3	4	19	28	40	56	70	88
4	5		29	41	57	71	90
5	6	20	30	42	58	72	
6			31	43		73	
7	7	21	32	44	59	74	
8	8	22	33	45		75	
9	9	23	34	46	60	76	92
10	10	24	35	47	61	77	94

	***Staphylococcus aureus* strain and SEQ ID No for SSL**						
SSL	N315	Mu50	MW2	NCTC 8325	EMRSA 16(252)	MSSA 476	COL
11	11	25	36	48	62	78	96
12	15			50	64	80	98
13	14			51	65	81	100
14	13			52	66	82	102

The SSL sequence employed may be one or more of SSL1 to SSL 14. In a preferred case where, for example, it is desired to use the sequence of an SSL9, the SSL9 will be have the sequence of one of the SSL9 indicated in Table 1 i.e. will be selected from SEQ ID Nos: 9, 23, 34, 46, 60, 76 and 92. In a preferred instance where is desired to employ the sequence of a SSL5, the SSL5 may be selected from the sequences of SEQ ID Nos: 6, 20, 30, 42, 58, and 72. In another preferred case, where it is desired to employ the sequence of a SSL 7, the SSL7 may be selected from the sequences of SEQ ID No: 7, 21, 32, 42, 59 and 74. Thus Table 1 indicates examples of preferred sequences for a particular SSL.

In a particularly preferred embodiment the SSL sequence employed may be SSL5, SSL7 and/or SSL9 and may preferably be one of the specific SSL 7 and SSL9 molecules whose sequence is provided herein. The SSL sequence may be a fragment of such a sequence. The SSL sequence employed may be a variant of the specific SSL 7 and SSL9 molecules whose sequence is provided herein or may be a variant of a fragment of such a sequence.

In some cases, the SSL employed may be an allelic form of an SSL as SSL genes from different *Staphylococcus aureus* strains vary in sequence. In some instances the SSL may be from one of the *Staphylococcus aureus* strains MW2, NCTC6571, FRI326 or NCTC8325, N315, Mu50, EMRSA 16(252), MSSA-476 or COL. In a particularly preferred embodiment the SSL may be from NCTC6571.

The targeting polypeptide may comprise a fragment of a naturally occurring SSL where the fragment retains the ability to target the targeting polypeptide to an antigen presenting cell. Such fragments may comprise subregions of any one or more of the sequences of any of SSL1 to SSL14 and in particular of the sequences provided herein of particular SSL1 to SSL14 molecules.

The targeting polypeptide may, for example, contain a sub-region of an SSL that is from 25 to 200, preferably from 35 to 175, even more preferably from 50 to 150 and even more preferably 75 to 125 amino acids in length. The targeting polypeptide may comprise a sub-region of an SSL that is 220 or less, preferably 180 or less, more preferably 160 or less, still more preferably 140 or less and even more preferably 120 or less amino acids in length. Such fragments may be derived from any SSL and in particular from the amino acid sequences indicated herein for SSL1 to SSL14. In some cases, the subregion may comprise at least 30, preferably at least 50,

more preferably at least 75 and even more preferably at least 100 amino acids from the SSL. In a preferred case the fragment may be from SSL5, SSL7 and/or SSL9. In a particularly preferred case the fragment may be from SSL9 and/or SSL7.

The targeting polypeptide may comprise a variant sequence of an SSL or a fragment thereof. Such variant sequences will be able to target themselves to antigen presenting cells. Any suitable variant polypeptide capable of directing the targeting polypeptide to an antigen presenting cell may be employed. In some cases, the variant will have at least 25%, preferably at least 30%, more preferably at least 35%, still more preferably at least 40% and even more preferably at least 45% amino acid sequence identity to an SSL and in particular to an amino acid sequence of any one or more of the specific sequences provided herein for SSL 1 to 14. Thus the variant may have the specified level of sequence identity with the equivalent SSL whose sequence is provided herein.

The level of amino acid sequence identity may be at least 50%, more preferably at least 55%, even more preferably at least 60% and still more preferably at least 65% amino acid sequence identity. The variant may, for example, have at least 75%, preferably at least 80%, more preferably at least 85%, still more preferably at least 90% sequence identity and even more preferably at least 95% sequence identity to an SSL and in particular to one or more of the specific SSL1 to 14 molecules whose sequence is provided herein.

In some cases the SSL employed may be an allelic variant of a known SSL gene including an allele of any of SSLs 1 to 14. Such variants may have a high degree of sequence identity to a known SSL allele and particular to one of those provided herein. Thus in some cases the variant may have at least 85%, preferably at least 95%, more preferably at least 97%, and even more preferably at least 99% sequence identity to any of the SSLs mentioned herein. The amino acid sequences of alleles of SSL5, SSL7 and SSL9 are indicated in Table 1 and the targeting polypeptide may comprise one or more of these sequences.

In instances where the targeting polypeptide comprises a variant sequence, the variant sequence may have one of the levels of sequence identity specified herein to more than one SSL. Thus, for example, the invention encompasses a variant of an SSL or a variant of a fragment of an SSL that has one of the specified levels of sequence identity to all of the SSLs whose sequence is provided herein or to a particular SSL. The sequence may have one of the specified levels sequence identity

to all of the alleles provided herein for a particular SSL whose sequence is provided herein.

In some cases a variant sequence may have one of the specified levels of sequence identity to at least two, preferably at least three, more preferably at least five and even more preferably at least six of the sequences provided herein for a particular SSL. In a preferred embodiment it will have one of the levels of sequence identity specified to all of the sequences provided herein for SSL5, SSL7 and/or SSL9. The variant may in particular have one of the specified levels of sequence identity to all of the sequences provided herein for SSL7 and/or SSL9. In a preferred case, the variant may have the specified level of sequence identity to the alleles from strain NCTC6571.1

The targeting polypeptide may comprise a variant sequence of a fragment of an SSL. Thus the fragment may be any of the lengths referred to herein. It may have any of the degrees of sequence identity referred to herein. In general a variant sequence may have the specified level of sequence identity over the whole of the variant, over at least 20, preferably at least 50, more preferably at least 75, and even more preferably over at least 100 amino acids. In the case of fragments, the sequence identity may be over any of the lengths specified herein and in particular over the entire fragment or targeting sequence. The variant or fragment has to be able to target the polypeptide to an antigen presentation cell. In cases where the targeting polypeptide comprises sequences, other than those responsible for targeting, the level of sequence identity may be over the region corresponding to the SSL, fragment thereof or variant of either. The specified level of sequence identity may be over the minimum region in the polypeptide necessary for targeting to the antigen presenting cell.

The variant may have amino acid substitutions in comparison to the normal sequence of the SSL. For example, it may have from 1, 2, 3 or more substitutions such as from 5 to 10, 10 to 20, 20 to 30 or more amino acid substitutions. The variant may have, in addition or alternatively, such numbers of amino acids deleted or inserted into it in comparison to the normal SSL. The amino acid changes may be conservative substitutions, for example according to the following Table. Amino acids in the same block in the second column and preferably in the same line in the third column may be substituted for each other.

ALIPHATIC	Non-polar	G A P
		I L V
	Polar-uncharged	C S T M
		N Q
	Polar-charged	D E
		K R
AROMATIC		H F W Y

The targeting polypeptide may comprise additional sequences to those responsible for targeting to an antigen presenting cell. In some cases the targeting polypeptide will consist essentially of the targeting sequences. In cases where there are additional sequences present, they may serve a variety of roles. In a particularly preferred embodiment, the targeting polypeptide will also comprise the antigen it is desired to target to the immune cells. The antigen may be any of those discussed herein.

Polypeptide sequences may be present which separate the various regions of the targeting polypeptide. For example, regions may be present to separate the region responsible for targeting from an antigen. Polypeptide sequences may be present which allow for purification of the polypeptide such as, for example, a histidine tag or an antibody recognition site. The targeting polypeptide may include an enzymatic cleavage site and in particular a protease recognition site may be present in the targeting polypeptide. It may be desirable to be able to remove sequences from the polypeptide such as those used to purify the polypeptide and cleavage sites may be employed.

The targeting polypeptide may lack specific sequences, for example because they have been cleaved after they are no longer of use. Thus in a preferred instance the targeting polypeptide may, for example, lack a Histidine tag and hence lack four, five, six, seven, eight, ten or more consecutive histidine residues typically at the terminus of the protein. The targeting polypeptide may lack an antibody recognition sequence used in purification, a reporter sequence and/or sequences such as thioredoxin or Pho A sequences. In some embodiments of the invention such sequences will not be present at any stage and will not be encoded by the nucleic acids of the invention.

The targeting polypeptide may comprise viral sequences. A targeting polypeptide of the invention may be used to target a viral particle to an antigen presenting cell. In such cases, the targeting polypeptide will typically be provided wholly or partially on the surface of the virus to allow the targeting sequence to target the virus to an antigen presenting cell. The targeting polypeptide may increase the affinity of the viral particle for the antigen presenting cell and may mean that the viral particle is more selective in binding to antigen presenting cells as opposed to other cell types.

The viral sequences may be, or comprise sequences from, surface proteins or polypeptide sequences which allow the targeting polypeptide to be displayed on the surface of the virus. The targeting polypeptide may comprise trans-membrane sequences to allow the targeting polypeptide to be present in a membrane and in particular in a viral membrane.

The targeting sequence may comprise linker sequences to allow different domains in the targeting polypeptide to function. In one case the targeting polypeptide may comprise a proline rich linker and in particular all or part of the proline rich sequence from the 4070A protein from a leukaemia virus surface protein. In cases where the targeting polypeptide is employed to target a viral particle to an antigen presenting cell the targeting sequences may be present in the targeting polypeptide together with the sequences necessary for fusion of the membranes of the virus and antigen presenting cell to allow entry of the virus into the cell.

The targeting polypeptide may comprise a protease cleavage site which will allow cleavage of the part of the targeting polypeptide and in particular a protease site which may be cleaved by a protease present on the surface of the antigen presenting cell.

In a preferred embodiment, the targeting polypeptide may comprise the sequence of SSL 5, 7, or 9 and in a particularly preferred case the sequence of SSL 7 or 9 may be employed. In some cases the sequence of SSL 7 may be employed, particularly where it is desired to target B cells such as $CD19^+$ B cells. In other cases, such as for example where it is not desired to target B cells, other SSLs may be employed and in particular SSL9 may be employed. In each case fragments of such sequence or variants of either may be employed including any of those referred to herein.

In a preferred embodiment of the invention the targeting polypeptide comprises:

(a) a SSL polypeptide having the amino acid sequence of any of SEQ ID Nos: 2 to 11, 13 to 15, 17 to 36, 38 to 48, 50 to 52, 54 to 66, 68 to 78, 80 to 82, 84, 86,88, 90, 92, 94, 96, 98, 100 and 102;

(b) a fragment of any of the sequences of (a), the fragment having the ability to target the complex to an antigen presenting cell; and/or

(c) a variant polypeptide having at least 30% amino acid sequence identity to any of the polypeptides of (a) or (b) and the ability to target the complex to an antigen presenting cell.

In another the targeting polypeptide comprises:

(a) the sequence of SEQ ID No: 7, 21, 32, 44, 59 and/or 74;

(b) a fragment of any of the sequences of (a), the fragment having the ability to target the complex to an antigen presenting cell; and/or

(c) a variant polypeptide having at least 70 % amino acid sequence identity to any of the polypeptides of (a) or (b) and the ability to target the complex to an antigen presenting cell.

In another the targeting polypeptide comprises:

(a) the sequence of SEQ ID No: 9, 23, 34, 46, 60, 76 and/or 92;

(b) a fragment of any of the sequences of (a), the fragment having the ability to target the complex to an antigen presenting cell; and/or

(c) a variant polypeptide having at least 70 % amino acid sequence identity to any of the polypeptides of (a) or (b) and the ability to target the complex to an antigen presenting cell.

In some cases a targeting polypeptide may comprise a plurality of sequences which individually would be able to lead to targeting to an antigen presenting cell. A minimal sequence necessary for targeting to an antigen presenting cell may be referred to as a targeting sequence. Such targeting sequences may be any of those discussed herein which have the ability to target a polypeptide to an antigen presenting cell. Thus a targeting polypeptide may comprise, for example, 1, 2, 3, 5 or more such targeting sequences. The targeting polypeptide may comprise any pair of those targeting sequences referred to herein. In some cases the targeting polypeptide may comprise different targeting sequences with different properties.

In some cases the targeting polypeptide will be employed to target a viral particle to an antigen presenting cell. Thus the targeting polypeptide collectively present on the virus will be able to increase the affinity and/or specificity of the viral particle for an antigen presenting cell in comparison to an equivalent virus lacking the targeting polypeptide.

Antigens

The targeting polypeptides of the invention are used to deliver a chosen antigen to an antigen presenting cell. The antigen may be any suitable antigen and typically will be a peptide or a polypeptide antigen. The antigen may, for example, be an antigen selected from a pathogenic antigen, an auto-antigen, an allergen and a cancer antigen

In some cases the invention may be used to deliver a nucleic acid molecule encoding an antigen to an antigen presenting cell. The nucleic acid may then be expressed in the antigen presenting cell to give rise to the antigen and presentation of the antigen. Thus the invention also encompasses the targeting of a nucleic acid molecule encoding any of the antigens mentioned herein to an antigen presenting cell.

In a preferred instance the antigen, may be an antigen from an infectious organism. The antigen may, for example, be derived from a virus, bacterium, parasite, protozoan, fungus, or prion. The antigen may be a surface antigen expressed on the surface of the pathogen or may be an intracellular antigen. The antigen may be from an intracelluar pathogen or alternatively an extracellular one.

The antigen may, for example, be from a bacterium. It may be from a gram positive or a gram negative bacterium. The antigen may, for example, be: an antigen

from *Mycobacterium* (for example from *Mycobacterium leprae, Mycobacterium tuberculosis, Mycobacterium avium, Mycobacterium intracellulare, Mycobacterium kansaii,* or *Mycobacterium gordonae*); *Pseudomonas*; *Yersinia*; *Salmonella* (for example from *Salmonella typhimurium*); *Helicobacter* (for example from *Helicobacter pylori*); *Borelia* (for example from *Borelia burgdorferi*); *Bordetella* (for example from *Bordtella pertussis* or *Bordetella parapertussis*); *Legionella* (for example from *Legionella pneumophilia*); *Staphylococcus* (for example from *Staphylococcus aureus*); Neisseria (for example from *Neisseria gonorrhoeae* or *Neisseria meningitides*); *Listeria* (for example from *Listeria monocytogenes*); or *Streptococcus* (for example from *Streptococcus pyogenes, Streptococcus agalactiae, Streptococcus viridans, Streptococcus faecalis, Streptococcus bovis,* or *Streptococcus pneumoniae*).

In some cases the antigen may be from: a *Campylobacter*; *Enterococcus*; *Haemophilus* (for example from *Haemophilus influenzae*); *Bacillus* (for example from *Bacillus antracis*); *Corynebacterium* (for example from *Corynebacterium diphtheriae*); *Erysipelothrix* (for example from *Erysipelothrix rhusiopathiae*); Clostridium (for example from *Clostridium perfringers*, or *Clostridium tetani*); Vibrio (for example Vibrio cholerae); *Enterobacter* (for example from *Enterobacter aerogenes*); *Klebsiella* (for example from *Klebsiella pneumoniae*); *Pasturella* (for example from *Pasturella multocida*); *Bacteroides*; *Fusobacterium* (for example from *Fusobacterium nucleatum*); *Streptobacillus* (for example from *Streptobacillus moniliformis*); *Shigella*; *Escherichia* (for example from *Escherichia coli*); *Rickettsia*; *Treponema* (for example from *Treponema palladium*); *Lactococcus; Lactobacillus; Brucella; Aeromona;, Franciesella; Citrobactor; Rhodococcus; Leishmania*; or *Strongylus* (for example from *Strongylus vulgaris).*

Examples of preferred bacterial antigens include: the *Shigella sonnei* form 1 antigen; the F1 antigen of *Yersinia pestis*; antigens from *Neisseria meningititidis* and in particular those encoded by the GNA33, GNA2001, GNA1220 and GNA1946 genes; the O-antigen of *V. cholerae* Inaba strain 569B; protective antigens of enterotoxigenic *E.coli*, such as fimbrial antigens including colonisation factor antigens, in particular CFA/I, CFA/II, and CFA/IV and the nontoxic B-subunit of the heat-labile toxin; pertactin of *Bordetella pertussis*, adenylate cyclase-hemolysin of *B. pertussis*; fragment C of tetanus toxin of *Clostridium tetani* and the LT (heat labile enterotoxin) and ST (heat stable toxin) antigens.

In some instances the antigen may be a viral antigen. The antigen may, for example, be a viral coat protein, glycoprotein or other proteins expressed on the surface of a virus. The antigen may be from a Picornaviridae (for example from a polio virus, a hepatitis virus, an enterovirus, a coxsackie virus, a rhinovirus, or an echovirus); Calciviridae ; Togaviridae (for example from a equine encephalitis virus or a rubella virus); Flaviridae (for example from a dengue virus, an encephalitis virus, or a yellow fever virus); Coronaviridae (for example from a coronavirus); Rhabdoviridae (for example from a vesicular stomatitis virus, or a rabies virus); Filoviridae (for example from an ebola virus); Paramyxoviridae (for example from a parainfluenza virus, mumps virus, measles virus, or a respiratory syncytial virus); Orthomyxoviridae (for example from an influenza virus such as influenza types A, B and C); Bungaviridae (for example from a Hanta virus, bunga virus, phlebovirus or a Nairo virus); Arena viridae (for example from a hemorrhagic fever virus) ; Reoviridae (for example a rotavirus); Birnaviridae; Hepadnaviridae (for example a Hepatitis B virus); Parvoviridae; Papovaviridae (for example from a papilloma virus, or polyoma virus); Adenoviridae; Herpesviridae (for example from herpes simplex virus (HSV) 1 or 2, varicella zoster virus, cytomegalovirus or a herpes viruses); Poxviridae (for example from a variola virus, vaccinia virus, or a pox virus); or an Iridoviridae (for example from African swine fever virus).

In a preferred case the antigen may be from a Retroviradae (e. g., HTLV-I ; HTLV-11; or HIV-1 (also known as HTLV-111, LAV, ARV, hTLR, etc.)). In a particularly preferred case the antigen may be one derived from HIV and in particular the isolates HIVIllb, HIVSF2, HTVLAV, HIVLAI, HIVMN ; HIV-1CM235, HIV-1; or HIV-2. In a particularly preferred embodiment, the antigen may be a human immunodeficiency virus (HIV) antigen. Examples of preferred HIV antigens include, for example, gpl20, gap 160 gp41, gag antigens such as p24gag and p55gag, as well as proteins derived from the pol, env, tat, vif, rev, nef, vpr, vpu or LTR regions of HIV. In a particularly preferred case the antigen may be HIV gp120 or a portion of HIV gp120. The antigen may be from an immunodeficiency virus, and may, for example, be from SIV or a feline immunodeficiency virus.

In a preferred case the viral antigen may be one from a hepatitis virus such as an antigen from hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), the delta hepatitis virus (HDV), hepatitis E virus (HEV) or hepatitis G virus

(HGV). In a particularly preferred embodiment the antigen may be from hepatitis B virus (HBV) and may preferably be a surface or core antigen from HBV.

In another preferred case the antigen may be from a herpesvirus family. Particular antigens include those from herpes simplex virus (HSV) types 1 and 2, such as HSV-1 and HSV-2 glycoproteins gB, gD and gH; antigens from varicella zoster virus (VZV), Epstein-Barr virus (EBV) and cytomegalovirus (CMV) including CMV gB and gH; and antigens from other human herpesviruses such as HHV6 and HHV7.

The antigen may be a fungal antigen, such as one from *Candida* or *Aspergilus*. In particular, it may be from *Candida albicans* or *Aspergillus fumigatus*. The antigen may be from *Sporothrix* (e.g from *Sporothrix schenckii*), *Histoplasma* (e.g. from *Histoplasma capsulatum*) *Cryptococcus* (e.g. from *Cryptococcus neoformans*) or *Pneumocystis* (e.g. from *Pneumocystis carinii*). The antigen may be from a parasitic pathogen and may, in particular, be from Taenia, Flukes, Roundworms, Amebiasis, Giardiasis, Cryptosporidium, Schistosoma, Pneumocystis carinii, Trichomoniasis and Trichinosis.

In some cases the antigen may be an antigen from a prion. In particular, the antigen may be one from the causative agent of kuru, Creutzfeldt-Jakob disease (CJD), scrapie, transmissible mink encephalopathy and chronic wasting diseases, or from a prion associated with a spongiform encephalopathy, particularly BSE. The antigen may be from the prion responsible for familial fatal insomnia.

In some cases the antigen may be from a parasitic pathogens including, for example, one from the genera *Plasmodium, Chtamydia, Trypanosome, Giardia, Boophilus, Babesia, Entamoeba, Eimeria, Leishmania, Schistosome, Brugia, Fascida, Dirofilaria, Wuchereria* and *Onchocerea*. Examples of preferred antigens from parasitic pathogens to be expressed as the heterologous antigen include the circumsporozoite antigens of *Plasmodium* species, such as the circumsporozoite antigen of *P. bergerii* or the circumsporozoite antigen of *P. falciparum*; the merozoite surface antigen of *Plasmodium* species; the galactose specific lectin of *Entamoeba histolytica*; gp63 of *Leishmania* species; paramyosin of *Brugia malayi*; the triose-phosphate isomerase of *Schistosoma mansoni*; the secreted globin-like protein of *Trichostrongylus colubriformis*; the glutathione-S-transferases of *Frasciola hepatica, Schistosoma bovis* and *S. japonicum*; and KLH of *Schistosoma bovis* and *S. japonicum*.

In some cases the antigen may be a cancer antigen and in particular a tumour antigen. Examples of particular cancers that the antigen may be derived include those from cancers of the lung, prostate, breast, colon, ovary, melanoma, a lymphoma and leukaemia. Examples of particular tumour antigens include MART-1, Melan-A, tyrosinase, p97, beta-HCG,GalNAc, MAGE-1, MAGE-2, MAGE-4, MAGE-12, MUC1, MUC2, MUC3, MUC4, MUC18, CEA, DDC, P1A, EpCam, melanoma antigen gp75, Hker 8, high molecular weight melanoma antigen,K19, Tyrl, Tyr2, members of the pMel 17 gene family, c-Met, PSA (prostate antigen), PSM (prostate mucin antigen), PSMA (prostate specific membrane antigen), prostate secretary protein, alpha-fetoprotein, CA125, CA19.9, TAG-72, BRCA-1 and BRCA-2 antigens.

The antigen may be an auto-antigen. In particular, the antigen may an antigen associated with an autoimmune disease. Auto-antigens include those associated with autoimmune diseases such as multiple sclerosis, insulin-dependent type 1 diabetes mellitus, systemic lupus erythematosus (SLE) and rheumatoid arthritis. The antigen may be one associated with, Sjorgrens syndrome, myotis, scleroderma or Raynaud's syndrome. Further examples of auto-immune disorders that the antigen may be associated with include ulcerative colitis, Crohns' disease, inflammatory bowel disorder, autoimmune liver disease, or autoimmune thyroiditis. Examples of specific autoantigens include insulin, glutamate decarboxylase 65 (GAD65), heat shock protein 60 (HSP60), myelin basic protein (MBP), myelin oligodendrocyte protein (MOG), proteolipid protein (PLP), and collagen type II. In cases where the antigen is an autoantigen the antigen will typically be administered in order to promote tolerance to the auto-antigen. Although in some cases models of the diseases may be produced using the invention to be produce an immune response.

In some cases the antigen may be an allergen. The allergenic antigen may be any suitable antigen from an antigen. For example, the allergen may be from *Ambrosia artemisiifolia*, *Ambrosia trifida*, *Artemisia vulgaris*, *Helianthus annuus*, *Mercurialis annua*, *Chenopodium album*, *Salsola kali*, *Parietaria judaica*, *Parietaria officinalis*, *Cynodon dactylon*, *Dactylis glomerata*, *Festuca pratensis*, *Holcus lanatus*, *Lolium perenne*, *Phalaris aquatica*, *Phleum pratense*, *Poa pratensis* or *Sorghum halepense*. The allergen antigen may be from a tree, such as, for example, from *Phoenix dactylifera*, *Betula verrucosa*, *Carpinus betulus*, *Castanea sativa*, *Corylus avellana*, *Quercus alba*, *Fraxinus excelsior*, *Ligustrum vulgare*, *Olea europea*, *Syringa vulgaris*, *Plantago lanceolata*, *Cryptomeria japonica*, *Cupressus arizonica*,

Juniperus oxycedrus, *Juniperus virginiana*, or *Juniperus sabinoides*. In some cases the antigen may be from an antigen from a mite such as, for example, from *Acarus siro*, *Blomia tropicalis*, *Dermatophagoides farinae*, *Dermatophagoides microceras*, *Dermatophagoides pteronyssinus*, *Euroglyphus maynei*, *Glycyphagus domesticus*, *Lepidoglyphus destructor* or *Tyrophagus putrescentiae*.

The allergen antigen may be from an animal such as, for example, from a domestic or agricultural animal. Examples of allergens from animals include those from cattle, horses, dogs, cats and rodents (e.g from rat, mouse, hamster, or guinea pig). In some cases the antigen may be from a food allergen and in others it may be from insect.

The antigen may be one involved in transplant rejection. The invention may be use to induce or promote tolerance to such an antigen in order to ameliorate or prevent transplant rejection.

Homologues of antigens may also be employed. Protein antigens employed may have homology and/or sequence identity with naturally occurring antigens, such as any of the antigens mentioned herein. They may have any of the levels of sequence identity or sequence changes specified herein.

The antigen may be a model antigen. The antigen may be one commonly used in experiments to assess immune responses. For example the antigen may be a lysozyme and in particular chicken egg lysozyme. The antigen may be ovalbumin and in particular chicken ovalbumin. Such model antigens may have the advantage that antigens, T cells and other reagents may be readily available for assessing antigen presentation by the targeted antigen presenting cell.

Complexes

The targeting polypeptides of the invention may be used to deliver a chosen antigen to antigen presenting cells (APCs). The targeting polypeptide and antigen are combined in the form of a complex. Thus a complex comprising a targeting polypeptide and an antigen is provided. In particular, the complex may comprise an antigen selected from a pathogenic antigen, auto-antigen, an allergen and a cancer antigen

In some cases a nucleic acid molecule encoding the antigen may be delivered to antigen presenting cells using the targeting polypeptides of the invention. Thus the invention also provides a complex comprising a targeting polypeptide and a nucleic

acid molecule encoding an antigen. The nucleic acid molecule will be delivered to the antigen presenting cell and result in expression of the antigen in the antigen presenting cell. Thus reference herein to an antigen includes a nucleic acid molecule encoding such an antigen.

A complex of the invention may comprise:

- a targeting polypeptide; and
- an antigen and/or a nucleic acid molecule encoding an antigen.

The targeting polypeptide and antigen may be joined together by any suitable means that ensures that the antigen is also targeted to the antigen presenting cell. Preferably, the targeting polypeptide and antigen may be present in the same polypeptide. Thus in some cases the antigen and targeting polypeptide may be directly fused to each other in a single polypeptide. In others the two may be present in the same polypeptide, but separated by an intervening sequence. For example, they may be separated by from 1 to 50, preferably from 5 to 25, more preferably from 10 to 20 amino acids.

In cases where the targeting polypeptide and fusion polypeptide are present in the same polypeptide, the targeting polypeptide may be separated by a sequence designed to be cleaved by a proteases in the antigen presenting cell in order to allow the two to be separated. In some cases where the targeting polypeptide and antigen are present in the same polypeptide, there may be a plurality of antigens in the polypeptide. For example, the same antigenic sequence may be repeated several times in the polypeptide such as from 1 to 50, preferably from 2 to 25, and more preferably from 5 to 10 times. In some cases the polypeptide may therefore comprise repeats of the same epitope or a group of epitopes from a particular antigen. In other cases different antigens may be present in the polypeptide. For example, two, three, four, five or more of any of the antigens mentioned herein may be present in the same polypeptide. The antigens may be from the same source or different source, and may, for example, be from different organisms.

The targeting polypeptide and antigen may not be part of the same polypeptide. For example, they may be joined together by other covalent means. The targeting polypeptide and antigen may be joined together by a covalent bond, such as a covalent bond between side chains, for example by disulphide bridges. The two may be joined by a linker or other bridging molecule. In some cases the targeting polypeptide and antigen may be provided or coated on a moiety and the complex

including the targeting polypeptide, antigen and moiety may be targeted to antigen presenting cells by virtue of the presence of the targeting polypeptide.

The complex may comprise a plurality of antigens and/or targeting polypeptides. For example, a plurality of antigens may be present and may be linked to a single targeting polypeptide or alternatively multiple antigens may be present in a polypeptide with a single targeting sequence. The complex, may for example comprise one, two, three, five, ten or more antigens. The complex may comprise antigens from different sources such as antigens from different organisms. The complex may comprise antigens from different strains of the same organism, such as from different strains of the same pathogen. In some cases the complex may comprise different allelic or mutant forms of the same antigen. For example, the antigens may be different forms of an antigen that display diversity that leads to strains of that pathogen with differing pathogenicity. The complex may comprise a plurality of copies of a single epitope where the epitope sequence is either present in the same polypeptide as the targeting polypeptide or is joined to it by one of the other means discussed herein.

The complex may comprise a plurality of targeting polypeptides. For example, the complex may comprise 1, 2, 3 or more targeting polypeptides, such as for example from 5 to 50, more preferably from 10 to 25 or even more preferably from 15 to 20 targeting polypeptides. The ratio of targeting polypeptides to antigen and/or epitope may be for example 1:1, 1:2, 1:5, 1:10 or 1:25, in some cases the ratio may be from 1:1 to 1:75, preferably from 1:2 to 1: 50 and more preferably from 1:5 to 1: 25. The ratio of targeting sequences to antigen and/or epitope may have such ratios.

In a particularly preferred embodiment of the invention the targeting polypeptides in the complex may be present in a dimeric form. This may be the case, for example, where the targeting sequence is, or is a fragment thereof or a variant of either of SSL7 and/or 7 and preferably of SSL 7. In a preferred case, where a fragment or variant is employed as well as having targeting activity it may be able to form a dimer.

The complex may be chemically modified, e.g. one or more, or indeed all, of the polypeptide types in the complex may be post-translationally modified. For example, they may be glycosylated or comprise modified amino acid residues. The polypeptides in the complexes and targeting polypeptides of the invention may

comprise amino acid analogs. In some cases, one or more peptides in the complex may have been generated synthetically.

In some cases libraries of different complexes may be generated. The libraries may comprise complexes with different antigens, for example, from different pathogens. In some cases, the library may comprise complexes with antigens from the same source, such as from the same organism including any of those mentioned herein. The libraries may be encoded by libraries of nucleic acids and/or vectors of the invention. Libraries may be generated and then screened to identify those complexes showing advantageous properties.

In some cases the complex may comprise a nucleic acid encoding the antigen rather than the antigen itself. In particular, the complex may comprise a nucleic acid molecule capable of expressing the antigen. Any of the sequences discussed herein for expressing polypeptides may be employed to express the antgen.

The invention therefore provides a viral particle which comprises a targeting polypeptide of the invention. In a particularly preferred instance the complex may comprise a viral particle which comprises:

(i) a targeting polypeptide;

(ii) a nucleic acid molecule encoding an antigen.

The targeting polypeptide will preferably be wholly or partially exposed on the surface of the viral particle to allow the virus to be targeted to an antigen presenting cell.

The complex may comprise the nucleic acid in any suitable manner to allow expression of the antigen in the antigen presenting cell. The complex may comprise a liposome with the targeting polypeptide present wholly or partially on the surface of the liposome to allow targeting to antigen presenting cells.

Nucleic acids

The present invention also provides a nucleic acid molecule comprising a polynucleotide sequence encoding a targeting polypeptide and an antigen and in particular an antigen selected from a pathogenic antigen, auto-antigen, an allergen and a cancer antigen.

The targeting polypeptide and antigen may be encoded by separate open reading frames (ORFs) or alternatively the nucleic acid may comprise an open reading frame encoding both the polypeptide and the antigen. In a preferred case, the

nucleotide sequence encoding the targeting polypeptide and the antigen are present in a single open reading frame.

In a particularly preferred embodiment the nucleic acid will be able to express the targeting polypeptide and antigen in the form of a polypeptide comprising both. As discussed elsewhere herein the targeting polypeptide and antigen may be directly fused or alternatively may be separated by intervening sequences which are also encoded by the nucleic acid.

The nucleic acid sequence may therefore encode any of the targeting polypeptides referred to herein. Thus the nucleic acid may comprise a sequence that encodes any of the SSLs, fragments thereof, or variants of either discussed herein. The nucleic acids may also encode any of the additional polypeptide sequences referred to herein. In a preferred case the nucleic acid molecule may comprise one or more of the polynucleotides sequences of SEQ ID Nos 1, 12, 16, 37, 49, 53, 63, 67, 79, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101 and/or 107. In particular, the nucleic acid may comprise one or more of the regions of SEQ ID Nos 1, 12, 16, 37, 49, 53, 63, 67, 79, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101 and/or 107 indicated herein to represent the CDS of a particular SSL. Thus any of the nucleic acid sequences provided herein which encode one or more of SSL1 to SSL14 may be used. The sequences used from the sequences provided herein may be restricted to the coding regions indicated or may also employ other regions from the gene and in particular the whole gene.

The nucleic acid may comprise the polynucleotide sequence of one or more of the coding sequences provided herein for SSL 1 to SSL14, a fragment of one or more of those sequence or a variant sequence of such a sequence or fragment, where the sequence encodes a targeting sequence able to target the encoded polypeptide to an antigen presenting cell.

The sequence of an SSL may be modified by nucleotide substitutions, insertions or deletions. In particular, the sequences provided herein which encode a SSL may be altered in such a way. The nucleic acid sequence may, for example, comprise from 1, 2, 5, 10 or 20 such substitutions, insertions and/or deletions as long as the encoded polypeptide has targeting activity. The variant sequence may comprise from 1 to 50, preferably from 5 to 25, more preferably from 10 to 15 amino acid insertions, deletions or substitutions as long as the encoded polypeptide displays targeting activity. Degenerate substitutions may be made and/or substitutions may be

made which would result in a conservative amino acid substitution when the modified sequence is translated, for example as shown in the Table above.

The nucleic acid may comprise a sequence that has at least 25%, preferably at least 30%, more preferably at least 35% and even more preferably at least 40% sequence identity to any one or more of SEQ ID Nos 1, 12, 16, 37, 49, 53, 63, 67, 79, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101 and/or 107. In particular, they may have such a level of sequence identity to the region encoding the SSL and/or over the whole gene.

In some cases the nucleic acid may have at least 50%, preferably at least 60%, more preferably at least 70%, even more preferably at least 80% sequence identity to such sequences. In other cases the level of sequence identity may be higher, because, for example, the sequence is a natural allelic variant or an engineered variant. Thus in some instances the sequence may have at least 85%, preferably at least 90%, more preferably at least 95%, even more preferably at least 97% and still more preferably at least 99% sequence identity to any of the sequences provided herein which encode SSL1 to SSL 14. In one case, the nucleic acid molecule will have one of the specified levels of nucleotide sequence identity to all of, three of, or two of the sequences encoding SSL5, SSL7 and/or SSL9 provided herein.

The levels of sequence identity specified may be over the entire sequence encoding the targeting polypeptide or targeting sequence. They may, for example, be over from 25 to 900 nucleotides, preferably over 50 to 700 nucleotides, more preferably over 75 to 350 nucleotides and even more preferably over 100 to 250 nucleotides. Thus in some cases the level of sequence identity specified may be over a region of at least 50, preferably at least 75, for instance at least 100, at least 150, more preferably at least 200 contiguous nucleotides or most preferably over the full length of the nucleic acid encoding the targeting sequence or polypeptide.

The nucleic acid may comprise the nucleotide sequence of one or more of the sequence SSL5, SSL7 and/or SSL9 genes whose sequence is provided herein, a fragment of any of the sequences or a variant of the preceding sequences where the encoded polypeptide displays targeting activity. In a preferred instance, the nucleic acid will comprise the nucleotide sequence of one or more of the sequences provided herein which encode SSL5, SSL7 and/or SSL9. In a preferred case the nucleic acid may comprise the nucleotide sequence of SEQ ID Nos: SSL7 and/or SSL9, a fragment of either or a variant of any such sequence, where the fragment or variant retains targeting ability. In a particularly preferred case the nucleic acid will comprise

the polynucleotide sequence of a sequence provided herein encoding SSL7 and/or SSL9.

Sequence identity and comparisons may be performed in a number of ways. For example the UWGCG Package provides the BESTFIT program which can be used to calculate homology (for example used on its default settings) (Devereux *et al* (1984) *Nucleic Acids Research* **12**, p387-395). The PILEUP and BLAST algorithms can be used to calculate homology or line up sequences (typically on their default settings), for example as described in Altschul (1993) J. Mol. Evol. 36:290-300; Altschul *et al* (1990) J. Mol. Biol. 215:403-10.

Software for performing BLAST analyses is publicly available through the National Centre for Biotechnology Information (http://www.ncbi.nlm.nih.gov/). This algorithm involves first identifying high scoring sequence pair (HSPs) by identifying short words of length W in the query sequence that either match or satisfy some positive-valued threshold score T when aligned with a word of the same length in a database sequence. T is referred to as the neighbourhood word score threshold (Altschul *et al*, 1990). These initial neighbourhood word hits act as seeds for initiating searches to find HSPs containing them. The word hits are extended in both directions along each sequence for as far as the cumulative alignment score can be increased. Extensions for the word hits in each direction are halted when: the cumulative alignment score falls off by the quantity X from its maximum achieved value; the cumulative score goes to zero or below, due to the accumulation of one or more negative-scoring residue alignments; or the end of either sequence is reached. The BLAST algorithm parameters W, T and X determine the sensitivity and speed of the alignment. The BLAST program uses as defaults a word length (W) of 11, the BLOSUM62 scoring matrix (see Henikoff and Henikoff (1992) *Proc. Natl. Acad. Sci.* USA 89: 10915-10919) alignments (B) of 50, expectation (E) of 10, M=5, N=4, and a comparison of both strands.

The BLAST algorithm performs a statistical analysis of the similarity between two sequences; see e.g., Karlin and Altschul (1993) *Proc. Natl. Acad. Sci.* USA 90: 5873-5787. One measure of similarity provided by the BLAST algorithm is the smallest sum probability (P(N)), which provides an indication of the probability by which a match between two nucleotide or amino acid sequences would occur by chance. For example, a sequence is considered similar to another sequence if the smallest sum probability in comparison of the first sequence to the second sequence is

less than about 1, preferably less than about 0.1, more preferably less than about 0.01, and most preferably less than about 0.001.

Any combination of the above mentioned degrees of sequence identity and minimum sizes may be used to define polynucleotides of the invention, with the more stringent combinations (i.e. higher sequence identity over longer lengths) being preferred. Thus, for example, a polynucleotide which has at least 90% sequence identity over 25, preferably over 30 nucleotides forms one aspect of the invention, as does a polynucleotide which has at least 95% sequence identity over 40 nucleotides.

The nucleic acids of the invention may comprise a number of another sequences in addition to that encoding the targeting polypeptide and antigen. For example, the nucleic acid may comprise sequences involved in the expression of the polypeptide it encodes such as those discussed below on the section in vectors. The nucleic acids may comprise primer sites, restriction sites, multiple cloning sites and other sequences to facilitate manipulation. The nucleic acid may comprise enhancer sequences to faciliate gene expression. The nucleic acid may comprise sequences allowing for the secretion of the encoded polypeptide or its targeting to a particular cellular compartment. In some cases the nucleic acids may also comprise a reporter gene or sequences, in other cases they may not.

The nucleic acids of the invention may be used in the production of targeting polypeptides, antigens and/or complexes of the invention. Such production may take place *in vitro, in vivo* or *ex vivo.* The polynucleotides may be used in recombinant protein synthesis or indeed as therapeutic agents in their own right. Polynucleotides encoding a targeting polypeptide and not an antigen or alternatively those encoding an antigen, but not a targeting polypeptide may be used to produce targeting polypeptide and/or antigen which can then be utilised to form complexes of the invention.

Vectors

The present invention provides vectors comprising a nucleic acid of the invention. Thus in one instance the invention provides a vector comprising a nucleic acid sequence that encode a targeting polypeptide of the invention and an antigen. The antigen may be one selected from any of those mentioned herein and in particular may be selected from a pathogenic antigen, auto-antigen, an allergen and a cancer antigen. The vector may comprise any of the nucleic acid sequences mentioned

herein. In a preferred instance, the vector may encode the targeting polypeptide and antigen via the same open reading frame (ORF).

The invention also provides vectors which comprise a nucleic acid which encodes the chosen antigen where the nuleic acid will be targeted to an antigen presenting cell using a targeting polypeptide of the invention. Such vectors will preferably be viral vectors.

The vector may, for example, be a cloning, expression and/or viral vector. The vector may, for instance, be a plasmid vector. The vector may be a viral vector. The vector may be a shuttle vector. The vector may comprise a selectable marker, for instance an antibiotic resistance selectable marker.

In particular, expression vectors are provided which are capable of expressing a targeting polypeptide of the invention and an antigen. In a preferred instance, the vector will express a targeting polypeptide of the invention as a fusion protein with the chosen antigen. Thus the vector may be capable of expressing a complex of the invention. Alternatively the targeting polypeptide and antigen may be produced separately and then linked to form a complex or the targeting polypeptide and antigen may be expressed as a single polypeptide and then further processing is carried out to produce a particular complex. For example, individual polypeptides may be linked together or sequences may be cleaved from the expressed polypeptides. In some case sequences used in purification may be removed by cleavage.

Expression vectors are routinely constructed in the art of molecular biology and may for example involve the use of plasmid DNA and appropriate initiators, promoters, enhancers and other elements, such as for example polyadenylation signals which may be necessary, and which are positioned in the correct orientation, in order to allow for protein expression. Other suitable vectors would be apparent to persons skilled in the art. By way of further example in this regard we refer to Sambrook *et al.*, 1989. The expression vector may be a prokaryotic or a eukaryotic expression vector. In some cases the expression vector may be used to produce the encoded protein *in vitro*. In other cases, the expression vector will be intended to generate *in vivo* expression of the encoded protein and may be used, for example, in a method of therapy.

Once coding sequences for desired proteins have been prepared or isolated, such sequences can be cloned into any suitable vector or replicon. Numerous cloning vectors are known to those of skill in the art, and the selection of an appropriate

cloning vector is a matter of choice. Ligations to other sequences may be performed using standard procedures, known in the art. The vector may be, for example, plasmid, virus or phage vectors provided with a origin of replication, optionally a promoter for the expression of the polynucleotide and optionally a regulator of the promoter. The vectors may contain one or more selectable marker genes.

Expression of the targeting polypeptide and/or antigen will typically be driven by a promoter. The promoter will usually be chosen on the basis of the cell the expression vector is to be used in. Thus for prokaryotic expression a prokaryotic promoter will typically be used, whilst for eukaryotic expression a eukaryotic or viral promoter will typically be employed. The promoter employed may be a viral or non-viral promoter. The promoter may be a mammalian promoter, such as a cell or tissue specific promoter or alternatively a promoter expressed in a wide range of cells. Other types of regulatory elements may also be present in the vector, for example, enhancer sequences.

Mammalian promoters, such as β-actin promoters, may be used. Tissue-specific promoters are especially preferred. Viral promoters may also be used, for example the Moloney murine leukaemia virus long terminal repeat (MMLV LTR), the rous sarcoma virus (RSV) LTR promoter, the SV40 promoter, the human cytomegalovirus (CMV) IE promoter, adenovirus, HSV promoters (such as the HSV IE promoters), or HPV promoters, particularly the HPV upstream regulatory region (URR). Viral promoters are readily available in the art.

In one preferred case the promoter employed may be one that is capable of being expressed in an antigen presenting cell. Thus a vector comprising a promoter capable of giving rise to expression of the antigen in an antigen presenting cell is provided. A promoter which is specific for antigen presenting cells may be employed.

Additional sequences may also be present in the open reading frame encoding the targeting polypeptide as well as optionally those encoding the antigen. In some cases, sequences directing secretion or release from the cell of the targeting polypeptide may be included. Peptide sequences allowing purification of the targeting polypeptide may be included. Preferably sequences allowing cleavage may be included and, for example, may be used to release the targeting polypeptide from the sequence used to purify the expressed polypeptide.

Cells

The invention provides cells comprising a polynucleotide or vector of the invention. Thus the invention provides for a cell comprising a polynucleotide and/or vector encoding a targeting polypeptide and an antigen. The targeting polypeptide and/or antigen may be any of those mentioned herein. Preferably, the cell will express the targeting polypeptide and antigen and in particular will express polypeptides comprising both. The cell may therefore be able to produce complexes of the invention and in one case may secrete them.

The invention also provides for cells that can produce viruses of the invention which have a targeting polypeptide provided on their surface either wholly or partially to allow for targeting of the viral particle to an antigen presenting cell. The invention provides a helper cell line that is capable of expressing the targeting polypeptide in such a way that it is incorporated in a viral particle. Such cells may also comprise the nucleic acid to be incorporated into the viral particles. The invention also provides cells infected with a virus of the invention.

Cells of the invention include transient, or preferably stable higher eukaryotic cell lines, such as mammalian cells or insect cells, produced using, for example, a baculovirus expression system, lower eukaryotic cells, such as yeast or prokaryotic cells such as bacterial cells. Particular examples of cells include mammalian cells such as HEK293T, CHO, HeLa and COS cells. The cells may be human cells. The cells may be, for instance, from any of the species and/or subjects mentioned herein. Preferably the cell line selected may be one which is not only stable, but also allows for normal post-translation modifications, particularly so that the antigen or epitope is in the form it would be naturally expected to be encountered as. The cell may, for example, allow normal glycosylation.

A polypeptide of the invention may be expressed in cells of a transgenic non-human animal. A transgenic non-human animal expressing a polypeptide of the invention is included within the scope of the invention. Such an animal may for example be a rodent (e.g. a mouse or rat). Preferred polypeptides of the invention may also be expressed in *Xenopus laevis* oocytes.

The sequences encoding the targeting polypeptide of the invention and/or the antigen may be introduced into a chosen cell by any suitable technique and may be generally referred to without limitation as "transformation". For eukaryotic cells,

suitable techniques may include calcium phosphate transfection, DEAE-Dextran, electroporation, liposome-mediated transfection and transduction using retrovirus or other virus, e.g. vaccinia or, for insect cells, baculovirus. For example, the calcium phosphate precipitation method of Graham and van der Eb, Virology 52:456-457 (1978) can be employed. General aspects of mammalian cell host system transformations have been described in U.S. Patent No. 4,399,216. For various techniques for transforming mammalian cells, see Keown *et al.*, Methods in Enzymology, 185:527 537 (1990) and Mansour *et al.*, Nature 336:348-352 (1988). Nucleic acids and vectors of the invention may be introduced into target cells both *in vitro* and *in vivo*. In particular, viral based systems may be used to introduce the nucleic acids and/or vectors of the invention into cells, particularly *in vivo*.

Antigen Presenting cells (APCs)

The invention allows a chosen antigen to be delivered to an antigen presenting cell. The targeting polypeptide present in the complexes direct the complex to an antigen presenting cell. The complex is taken up by the antigen presenting cell. This means that the antigen may then be presented by the antigen presenting cell.

The invention also provides for the delivery of a nucleic acid molecule encoding an antigen through the use of a targeting polypeptide of the invention. The targeting polypeptide will preferably be on the surface of a virus. Infection of the antigen presenting cell by the virus results in the production of antigen which may then be presented by the cell.

The antigen presenting cell may be any suitable antigen presenting cell. In particular, it may be a professional antigen processing cell and will typically express MHC molecules. The antigen processing cell will typically express MHC II molecules and the complex will allow the chosen antigen, or peptides derived from it, to be presented via MHC II molecules. In some cases the antigen, or peptides derived from it, may be presented via MHC I. The antigen may be presented by both MHC I and II, typically presentation will be via MHCII. Examples of MHC I and II molecules which may be involved in presentation include HLA-A2, HLA-B62, HLA-Bw62, HLA-B35, HLA-DRB1, HLA-DRB2, HLA-DRB3, HLA-DRB5, HLA-DRB7, HLA-A25, HLA-B8, HLA-B52, HLA-DQB1, HLA-A3, HLA-A11 or HLA-B27.

Examples of antigen presenting cells that the invention may be used to target antigens to include dendritic cells, monocytes, and/or or a B cells. In particular,

monocytes and/or dendritic cells may be targeted and in a preferred instance the antigen presenting cell is a dendritic cell. The B cells may typically be $CD19^+$ B cells. The monocytes may, for example, be $CD14^+$ cells and such cells may also be $CD2^{lo}$ cells.

In cases where the antigen presenting cell is a dendritic cell it may express cell surface markers known to be characteristic of dendritic ells. In particular the dendritic cell may express CD11c, CD209 (also known as DC sign) and/or CD13. The cell may be $CD14^{lo}$. In some cases the cell may express all of CD11c, CD209 and CD13 and may also be $CD14^{lo}$.

In a preferred instance the antigen presenting cell may be a dendritic cell. Any type of dendritic cell may be targeted. Examples of dendritic cells include a monocyte derived dendritic cell, a plasmacytoid derived dendritic cell or an intersititial dendritic cell. The dendritic cell may be a langerhans cell. The dendritic cell may be one present in an organ or tissue. The dendritic cell may be one from, or present in, a mucosal surface. The dendritic cell may be an intestinal dendritic cell such as one obtained from Peyers patches. The dendritic cell may be one present in, or obtained, from an immune tissue such as from a secondary lymph node. The dendritic cell may be present in, or obtained from the spleen or a lymph node.

The term antigen presenting cell covers any cell that can present an antigen targeted to it via a complex of the invention. In some cases antigen presenting cells may have different stages in their development during which they, for example, predominately take up antigen, rather than present it. For example, it is thought that dendritic cells may have immature stages characterised by the uptake of large amounts of potential antigens and more mature stages characterised by lower amounts of antigen uptake, but increased amounts of antigen presentation of the antigens they acquired earlier. The dendritic cell may, for example, be present in the periphery and effectively collect antigen and then move to areas such as secondary lymphoid tissues to present antigens. In one case the invention encompasses targeting of an antigen to an immature antigen presenting cell subsequently capable of presenting the antigen it has taken up, such as to an immature dendritic cell.

In some cases it may be desirable to target immature dendritic cells in instances where it is desired to induce tolerance. In particular, delivery of antigen by employing a targeting polypeptide of the invention in the absence of a stimuli which induces or promotes dendritic cell maturation can result in tolerance. To achieve

tolerance the targeting polypeptide may preferably be used to deliver the chosen antigen or nucleic acid encoding the antigen in the absence of an adjuvant. An advantage of employing the targeting polypeptide of the invention to induce tolerance is that unlike many methods for inducing tolerance a large dose of antigen is not required. Steinman *et al* (2003) Ann. Rev. Immunol., 21:685-711 discusses the induction of tolerance via dendritic cells and the methods and assays discussed therein may be employed when inducing tolerance using the methods of the invention. In situations where it is desired to induce tolerance peripheral dendritic cells may preferably be targeted.

Conversely, in situations where it is desired to promote an immune response against the antigen, the targeting polypeptide may preferably be employed with an adjuvant and in particular one which induces or promotes stem cell maturation such as aluminium hydroxide.

In some cases the antigen cells may be manipulated *in vitro* and this may allow control of whether the cells are exposed to stimuli which promote dendritic cell maturation. Thus by ensuring that the cells are not exposed to stimuli responsible for inducing maturation the resultant cells may be used to induce tolerance. In other cases the cells will be exposed to stimuli which promote dendritic cell maturation and hence the cells can be used to promote an immune response when they are transferred to a subject.

Antigen presenting cells may be isolated from any suitable source including any of those mentioned herein. For example, such cells may be isolated from the white cells of the blood. Methods based on cell density such as LYMPHOPREP™ and centrifugation may be employed. The cells may be isolated using a variety of techniques including antibody based techniques. The cells may be isolated using negative and positive selection techniques based on surface markers which present and/or those that are not present on antigen presenting cells. In some cases, antigen presenting cells may be obtained by exposing other cells, such as precursor cells, to appropriate stimuli.

Dendritic cells may be obtained by treating monocytes with appropriate stimuli such as GM-CSF and/or IL-4. For example, cells may be culture in the presence of 10 to 500 ng/ml, preferably from 25 to 200 ng/ml, more preferably from 50 to 150 ng/ml and even more preferably in the presence of 100 ng/ml GM-CSF. In particular, human and preferably recombinant human GMCSF may be employed. The

cells may be cultured in the presence of 10 to 250 ng/ml, preferably from 25 to 150 ng/ml, more preferably from 40 to 70 ng/ml and even more preferably in the presence of 50 ng/ml IL-4. T and B lymphocytes may be removed by appropriate selection such as on the basis of the markers CD3, CD2 and/or CD19.

In other cases plasmacytoid cells may be induced to differentiate into dendritic cells by exposure to IL-3. In some instances immature antigen presenting cells may be induced to mature using appropriate stimuli. Such treatments will typically be performed *in vitro*.

The antigen presenting cells may be treated *ex vivo*. Thus the cells may be recovered from a subject loaded with antigen using the methods of the invention and then used therapeutically. The invention provides loaded antigen presenting cells. The invention provides antigen presenting cells which have been infected by a viral particle of the invention.

Assays

The targeting polypeptides of the invention are utilised to target antigens to antigen presenting cells. This targeting ability and the downstream effects of targeting can be assessed in a number of ways.

The ability of a polypeptide to target itself, and hence a complex, to an antigen presenting cell can be assessed using any suitable technique. In one case *in vitro* assays may be performed to monitor binding of the targeting polypeptide to an antigen presenting cell. The targeting polypeptide may be labelled and the binding to the antigen presenting cell followed. The targeting polypeptide may be labelled with a fluorochrome and its binding to an antigen presenting cell assessed using techniques such as flow cytometry. Binding at 4°C and 37 °C may be compared to help demonstrate that the binding is specific.

The ability of the polypeptide under study to target to an antigen presenting cell may be compared with a polypeptide known to have targeting ability. For example, where the test targeting polypeptide is based on the sequence of a particular SSL the ability to compete against that SSL may be compared using two or more different labels. The ability of a targeting polypeptide to compete against varied concentrations of a polypeptide with known binding activity may be measured. In this way polypeptides with binding activity may be identified and the level of targeting ability that they display quantified. Such assays will typically be performed *in vitro*

but the ability of antigen cells *in vivo* or *ex vivo* conditions to take up test polypeptides and/or complexes may also be measured. Again, labelling may be used to study delivery to antigen presenting cells.

The ability of a targeting polypeptide to enter the antigen presentation pathway may also be assessed. The presence of the targeting polypeptide in a subcelluar compartment associated with antigen presentation may be measured. Labelling may be used to achieve this. Confocal microscopy can be used to confirm that the label, and hence the targeting polypeptide, has entered the cell. Stains for subcellular compartments associated with antigen presentation may be employed. For example, Texas red dextran staining may be employed to identify such compartments and co-staining may be used to confirm the presence of the targeting polypeptide in such compartments. In addition, the association of the complex, or part of it, in the same regions as MHC molecules, particularly MHC II may be examined.

The ability of a particular targeting polypeptide to lead to antigen presentation may be studied. Thus the presence of peptide sequences from the antigen being presented on the cell surface by MHC may be studied. In particular, presentation by MHCII may be examined. Techniques may be used to elute peptides bound to MHC and identify those originating from the chosen antigen. The degree of peptide presented when the antigen is provided on its own and when it is provided as part of a complex may be compared. The ability of particular polypeptides to lead to antigen presentation may be compared including using control polypeptides with known targeting ability. Thus the ability of two polypeptides to lead to presentation of the same antigen may be compared.

In some assays the downstream effects of antigen presentation may be measured. Thus assays may involve an antigen presentation cell being loaded using test polypeptides and then antigen presentation to a second cell may be measured. The ability of different targeting polypeptides and complexes to bring about the downstream effects of antigen presentation may be measured including controls with known activity. Such assays may be performed *in vitro* and, for example, they may be performed using an antigen presenting cell and a T cell known to have a receptor specific for an epitope present in the antigen. The T cell may be any suitable T cell. It may be a $CD4^+$ or $CD8^+$ T cell and in particular may be a $CD4^+$ T cell. The downstream effects of antigen presentation may also be measured *in vivo*

Downstream effects of antigen presentation include activation of the T cell. Various signal transduction effects associated with activation of the T cell may be measured. The activation may include the differentiation and/or proliferation of the T cell. Thus the number and proliferation of the T cells may be measured, using, for example, suitable labelling techniques or by measuring cell number. The expansion of particular subsets of T cells may be measured. For example, by flow cytometry. Assays involving autologous and/or allogenic T cells may, for instance be employed, including any of those mentioned herein.

The activation of the T cells may lead to the release of cytokines. For example, the activation may lead to the release of interleukins (e.g. Il-2, IL-4 , IL-5, IL-6 and/or IL-10) , IFNγ and/or TNF-β. In some cases antigen presentation may lead to a Th1 type response. Thus the cytokines released may be, or predominately be, IL-2, IFNγ and/or TNF-β. In other cases the response may be a Th2 type response. The cytokines released may be, or predominately be, IL-3, IL-4, IL-5, IL-6 and/or IL-10. The T cells may release factors that stimulate their own proliferation such as IL-2. and/or IL-4. Particular complexes and substances of the invention may be designed to give particular responses such as any of those mentioned herein. The release of such factors can be studied both *in vitro* and *in vivo* using techniques such as ELISA to measure levels of such compounds. In some cases, the cytokine levels measured may be one or more, or indeed all, of IFNγ, IL-10 and IL-13.

The presence and/or number of effector T cells and memory T cells may be assessed. In addition various downstream effects may be measured. The number and activity of $CD4^+$ and/or $CD8^+$ T cells may be measured and in particular those specific for the chosen antigen. Antibody responses may be assessed in terms of the amount and types of antibody produced. In one preferred instance, the delivery of the chosen antigen using the targeting sequences of the invention leads to an antibody response against the chosen antigen. Any of the assays discussed herein may, for instance, be used to detect such an antibody response. In some cases tolerance may be induced and an antibody response may not be seen and in particular subsequent challenge with the antigen may result in a lower response or no response in comparison to the response seen without the initial induction of tolerance.

The effects on other immune cells may be measured such as on macrophages and/or granulocytes. The skilled person will be aware of appropriate assays for assessing the immune response and immunogenicity.

In some embodiments of the invention a nucleic acid encoding an antigen, rather than the antigen itself, is targeted to the antigen presenting cell. In a particularly preferred embodiment the viral particles comprising targeting polypeptides may be employed in the invention. The ability of the viruses to selectively bind to antigen presenting cells may be measured. Non-antigen presenting cells may be employed as controls to assess the specificity of the viruses.

Standard techniques may be used to monitor the expression of the nucleic acids targeted to antigen presenting cells. For example, test experiments may be done using reported genes in place of an antigen encoding gene. Techniques such as RT-PCR, Northern blotting, Western Blotting and cell staining may be used to monitor expression in antigen presenting cells. Presentation of the antigen may be evaluated.

The above techniques may be used to identify effective targeting sequences. They may also be used to assess the efficacy of the invention in promoting an immune response against a chosen antigen. The techniques may also be used to assess the efficacy of the substances of the invention in the treatment or prevention of any of the conditions referred to herein. Typically suitable controls will be employed. In some cases standard test antigens and/or targeting polypeptides may be employed and compared to the substance under test.

Loading antigen presenting cells

The invention provides for the loading of antigen presenting cells. Thus the invention provides a method of loading an antigen presenting cell, comprising contacting an antigen presenting cell with a complex of the invention. The targeting polypeptide present in the complex directs the complex to the antigen presenting cells. The complex is taken up by the antigen presenting cell and the antigen is presented by the antigen presenting cell as discussed herein. The targeting of the complex to the antigen presenting cell is termed loading of the antigen presenting cell.

The invention also encompasses the loading of antigen presenting cells using a targeting polypeptide of the invention to deliver a nucleic acid encoding an antigen to antigen presenting cells. In particular viral particles comprising the targeting polypeptide may be employed. The invention therefore provides a method of loading an antigen presenting cell comprising using a targeting polypeptide of the invention to deliver a nucleic acid molecule encoding an antigen to the antigen presenting cell. The

invention provides for the infection of an antigen presenting cell with a virus of the invention.

The loading of antigen presenting cells or their precursors may be performed *in vitro, ex vivo* or *in vivo*. In the case of *in vitro* loading the antigen presenting cell may simply be contacted with a complex of the invention. The cell may be cultured in the presence of the complex under suitable conditions. The cell and complex may, for example, be contacted for between five minutes and ten days, preferably from an hour to five days, more preferably from five hours to two days and even more preferably from twelve hours to one day. *Ex vivo* loading may,for instance, be carried out in the same manner once the cells to be loaded have been obtained.

Loading of antigen presenting cells or their precursors may be performed *in vivo*. Thus the invention provides an *in vivo* method of loading antigen presenting cells comprising administering to a subject and effective amount of a complex of the invention. Administration may be via any of the routes discussed herein. Loading *in vivo* may also be achieved by administering a nucleic acid, vector, cell, virus, vaccine or pharmaceutical composition of the invention. The administration of such products results in complexes of the invention coming into contact with antigen presenting cells. Thus the nucleic, vector, virus or cells may lead to the production of a complex of the invention which then loads an antigen presentation cell present in the subject.

In one case antigen presenting cells recovered from a subject are loaded *in vitro* with a complex of the invention. The invention therefore provides an *ex vivo* method of loading antigen presenting cells. The loaded cells may then be returned to a subject and in particular to promote an immune response against the antigen that the cells have been loaded with.

The invention also provides antigen presenting cells which have been loaded using the complexes of the invention. Such antigen presenting cells will typically comprise the complex or breakdown products of the complex and in particular the antigen to be presented. The loaded cells may comprise epitopes of the antigen. The cell may also comprise the targeting polypeptide and/or breakdown products thereof. The invention provides such cells in an isolated form. The loaded cells may comprise a nucleic acid of the invention and in particular may comprise a viral vector of the invention. Preferably, the viral vector will be replication deficient.

Generally the antigen presenting cell of the invention carries peptides, and in particular an antigenic epitope, derived from the chosen antigen on its surface in

conjunction with an MHC class I or class II molecule and in particular in conjunction with an MHC II molecule. In one embodiment the antigen presenting cell has at least 100, preferably at least 200, for example at least or about 500 or 1000, class I and/or class II molecules on its surface loaded with the product and in particular class II molecules. In some cases, the cells may carry a label or be labelled, such as, for example, with thymidine or radioactive chromium. The invention also provides T cells that have been activated by a loaded antigen presentation cell of the invention.

In some cases antigen presenting cells may be recovered from a subject, loaded *in vitro* and then returned to the same subject. In other cases, it may be that T cells are recovered from a subject, exposed to loaded antigen presenting cells of the invention *in vitro* and then returned to the subject.

In one case the invention may provide a composition comprising T cells, antigen presenting cells and a complex of the invention. The T cells or antigen presenting cells may be any of the cells mentioned above. In particular, the antigen presenting cells may be dendritic cells. The T cell:antigen presenting cell ratio may be typically from 500:1 to 1:500. Typically at least 10^3, such as (e.g. at least or about) 10^5, 10^6, 10^7, 10^8, 10^9 cells are present per millilitre of the composition. The composition typically also comprises a culture medium capable of supporting the T cells or antigen presenting cells, such as RPMI medium. The medium may also comprise cytokines, such as IL-2, IL-4, IL-7 or TNF-α. The T cells and antigen presenting cells may be from the same individual.

The cells employed in the invention, particular the antigen presenting cells and/or T cells, may be autologous cells, or cells which have been partially or fully matched with the subject for MHC class I HLA-A or HLA-B; and/or for MHC class II type. In a preferred case, the cells employed in the invention may be recovered from a subject and utilised *ex vivo* and subsequently returned to the same subject.

Delivery of nucleic acid molecules encoding antigens to antigen presenting cells

The targeting polypeptides of the invention may be used to deliver a nucleic acid molecule which encodes an antigen to an antigen presenting cell. The nucleic acid molecule gives rise to expression of the antigen in the antigen presenting cell and to the subsequent presentation of the antigen by the cell.

The nucleic acid molecule will preferably comprise a promoter which is operably linked to the sequences encoding the antigen and which is active in antigen presenting cells or which can be induced in antigen presenting cells.

In a particularly preferred embodiment the nucleic acid encoding the antigen may be delivered to the antigen presenting cell via a viral particle which comprises a targeting polypeptide of the invention. The targeting polypeptide will typically be provided wholly or partly on the surface of the virus in order for the polypeptide to be able to target the virus to an antigen presenting cell.

Any suitable virus may be used in such embodiments. The virus may, for example, be a retrovirus, a lentivirus, an adenovirus, an adeno-associated virus , a vaccinia virus or a herpes simplex virus. In a particularly preferred embodiment the virus may be a lentivirus. The lentivirus may be a modified HIV virus suitable for use in delivering genes. The lentivirus may be a SIV, FIV, or equine infectious anemia virus (EQIA) based vector. The virus may be a moloney murine leukaemia virus (MMLV).

The targeting polypeptide may comprise sequences from the virus. For example, the targeting polypeptide may comprise sequences from a viral surface protein. In particular, the targeting sequences may be at the N terminus of the targeting polypeptide and be fused or linked to surface protein sequences. The targeting polypeptide may also comprise a transmembrane domain so that is can be provided in the viral membrane.

In a particularly preferred embodiment the targeting polypeptide may include sequences from a surface protein of the virus. In particular the targeting polypeptide may comprise sequences from a surface protein that is involved in the normal binding of the virus to its target cell. The binding of the targeting polypeptide to the antigen presenting cell may lead to conformational changes allowing the viral surface protein sequences to bind to their target on the cell surface. This may lead to fusion of the viral and cell membranes allowing entry of the virus into the antigen presenting cell. Thus the targeting sequences and surface protein domains may show receptor cooperation to facilitate the entry of the virus specifically into the antigen presenting cells. The targeting polypeptide may include linker sequences which facilitate the co-operation and in particular proline rich sequences present in the viral surface protein may be employed. The proline rich linkers discussed in Martin *et al* (2003) Journal of

Virology 77(4): 2753-2756 and Valsesia-Wittmann *et al* (1997) EMBO Journal, 16(6): 1214-1223 may be employed.

The invention provides a virus comprising a targeting polypeptide as well as a cell infected by such a virus. The virus will typically also comprise a nucleic acid molecule encoding the chosen antigen. The virus may, for instance, be any of those mentioned herein. The nucleic acid molecule may also encode other sequences, for example the nucleic acid sequences may comprise sequences which express proteins which boost the immune response to the antigen. The nucleic acid may encode a cytokine, including any of those mentioned herein and in particular IL-1, IL2 and/or IL12. The nucleic acid may also encode a costimulatory molecule such as a surface polypeptide which enhances the immune response. The nucleic acid may encode, for example, CD80 and/or CD86.

The viruses of the invention are preferably replication deficient. In some cases the nucleic acid sequences encoding the targeting polypeptide will not be included in the viral vector. Thus the invention also provides helper cells which express the targeting polypeptide in such a way that the targeting polypeptide is incorporated into the viral particles. The invention also provides nucleic acid vectors that encode a targeting polypeptide of the invention which comprises viral sequences.

Medicaments, methods and therapeutic use

The complexes of the invention and various related aspects of the invention may be used be used in a method of therapy of the human or animal body. Thus the invention provides for the use of a targeting polypeptide, a complex, a nucleic acid, a vector, a cell, a virus, or an antigen presenting cell of the invention in a method of treatment of the human or animal body by therapy.

The invention provides for the use of a complex of the invention, a nucleic acid encoding a targeting polypeptide and antigen of a complex of the invention, a vector comprising such a nucleic acid, a cell comprising such a nucleic acid or vector, a virus of the invention or an antigen presenting cell of the invention in the manufacture of a medicament for use in immunisation.

In a preferred case the invention provides for the use of a complex comprising:

(a) a targeting polypeptide comprising a staphylococcal superantigen-like

protein (SSL), a fragment thereof or a variant of either, where the SSL, fragment or variant has the ability to target the complex to an antigen presenting cell; and

(b) an antigen or a nucleic acid encoding an antigen,

in the manufacture of a medicament for use in immunisation.

In some instances the antigen comprises a polypeptide which is present in the complex as a fusion polypeptide with the targeting polypeptide. In others the antigen and targeting polypeptides are not part of the same polypeptide, but are covalently joined to each other or are joined through a linker. In a preferred case the antigen is a pathogenic antigen, an auto-antigen, an allergen and/or a cancer antigen. In another, the targeting polypeptide is present as a dimer.

Immunisation may result in promoting an immune response against the chosen antigen. Any of the effects resulting from targeting antigen presenting cells mentioned herein may be promoted or achieved. In particular the level of presentation of the chosen antigen will be increased. An increase in presentation via MHC I and/or MHC II molecules and in particular via MHC II molecules may be seen. In a preferred case the level of antigen presentation achieved may be such that when the same antigen is encountered again an increased immune response is seen in comparison to if the initial immunisation had not taken case. In particular a therapeutic and/or protective immune response may be raised. The invention may therefore ensure that a higher level of immune response is seen when the antigen is next encountered.

The invention may be used to enhance the level of antigen presentation or of any of the downstream effects thereof, such as any of those mentioned herein, in comparison to administration of an equivalent amount of antigen in the absence of a targeting polypeptide. The increase may be double, treble, or more fold, in some cases it may be at least ten-fold, preferably at least twenty-fold and even more preferably at least 100 fold, or 1000 fold or more. It may be that a protective, or therapeutic response, is seen whereas in the absence of the use of a targeting polypeptide it is not.

The invention also provides for an agent for immunising a subject, the agent comprising a complex of the invention, a nucleic acid encoding a targeting polypeptide and antigen of a complex of the invention, a vector comprising such a

nucleic acid, a cell comprising such a nucleic acid or vector, or an antigen presenting cell of the invention.

The various diseases and conditions to be prevented or treated may be any of those mentioned herein or associated with an antigen mentioned herein. In particular, the disease may be one associated with a pathogen, such as a bacterium, virus, bacterium, parasite, protozoan, fungus, and/or prion. In some cases the disease may be a cancer such as any of those mentioned herein.

In some instances the invention will be used to induce tolerance to a particular antigen and in particular to an allergen or an auto-antigen In such cases typically the method will involve the delivery of the desired antigen to an antigen presenting cell in the absence of a stimulus which promotes antigen presenting cell maturation. In particular, the antigen may be delivered in the absence of an adjuvant such as aluminium hydroxide. The immunisation methods and vaccines of the invention may be used to induce tolerane to a selected antigen.

The substances of the invention may be administered to any suitable subject. The subject on which the method of the invention is performed is generally a vertebrate subject. By "vertebrate subject" is meant any member of the subphylum cordata, particularly mammals, including, without limitation, humans and other primates, as well as rodents, such as mice and rats. The subject may be a non-human animal. The non-human animal may be a domestic animal or an agriculturally important animal. The animal may be a domestic pet. The animal may be a monkey such as a non-human primate. The term subject does not denote a particular age. Thus, both adult and newborn individuals are intended to be covered. In one embodiment the subject is susceptible to or at risk from the relevant disease. For example, the subject may have been exposed, or will be in a region where there is a risk of exposure, to a particular antigen and in particular a pathogen.

The invention also covers the use of the complexes of the invention to promote antigen presentation of a chosen antigen. In some cases the invention may be used to bring about antigen presentation in an animal model, for example to study whether or not a particular immune response can be raised. The efficacy of the invention may be assessed in such non-human animal models. In some cases the invention may be used to help generate an immune response in a non-human animal in order to obtain antibodies against a chosen antigen that can then be recovered. Thus the invention may be used in a method of antibody production.

The invention may be used in combination with other means of, and substances for, immunisation. In some cases the complexes of the invention may be administered simultaneously, sequentially or separately with antigen which is not part of a complex of the invention. Thus complexes may be administered with the same antigen in a form not linked to a targeting polypeptide. The substances of the invention may be used in combination with existing vaccines for a particular antigen and may, for example, be simply mixed with such vaccines. Thus the invention may be used to increase the efficacy of existing vaccines including, for example, peptide, polypeptide, nucleic acid, viral and/or bacterial based antigens.

Pharmaceutical compositions, vaccines and administration

The invention additionally provides pharmaceutical compositions comprising a complex, nucleic acid, vector and/or cell of the invention and a pharmaceutically acceptable carrier or diluent. The present invention also provides a vaccine composition comprising a complex, nucleic acid, vector and/or cell of the invention. The vaccines and compositions may comprise any of the substances mentioned herein and in particular the complexes, nucleic acid molecules, vectors, viruses and cells of the invention. The invention provides a method of vaccination comprising administering to a subject an effective amount of a vaccine composition of the invention.

The various compositions, vaccines and other substances of the invention may be formulated using any suitable method. Formulation with standard pharmaceutically acceptable carriers and/or excipients may be carried out using routine methods in the pharmaceutical art. For example, an active substance may be dissolved in physiological saline or water for injections. The exact nature of a formulation will depend upon several factors including the particular substance to be administered and the desired route of administration. Suitable types of formulation are fully described in Remington's Pharmaceutical Sciences, 19th Edition, Mack Publishing Company, Eastern Pennsylvania, USA, the disclosure of which is included herein of its entirety by way of reference.

The substances may be administered by enteral or parenteral routes such as via oral, buccal, anal, pulmonary, intravenous, intra-arterial, intramuscular, intraperitoneal, topical or other appropriate administration routes. The substances may in some cases be administered to sites characterised by the presence of antigen

presenting cells. In cases where loaded antigen presenting cells are administered they may be administered, for example, to sites of antigen presentation such as secondary lymph nodes.

Vaccines may be prepared from one or more of the complexes, nucleic acids, vectors, and/ or cells of the invention together with a physiologically acceptable carrier or diluent. Typically, such vaccines are prepared as injectables, either as liquid solutions or suspensions; solid forms suitable for solution in, or suspension in, liquid prior to injection may also be prepared. The preparation may also be emulsified, or the encapsulated in a liposome, particularly in the case of nucleic acids and vectors of the invention. The active ingredient may be mixed with an excipient which is pharmaceutically acceptable and compatible with the active ingredient. Suitable excipients are, for example, water, saline, dextrose, glycerol, ethanol, of the like and combinations thereof.

In addition, if desired, the vaccine and/or pharmaceutical compositions of the invention may contain minor amounts of auxiliary substances such as wetting or emulsifying agents, pH buffering agents, and/or adjuvants which enhance effectiveness.

The complexes of the invention enhance the immunogenicity of a chosen antigen. They may therefore act as adjuvants for a chosen antigen and may be used as adjuvants. In some cases other adjuvants may be present in the various formulations of the invention or be administered simultaneously, separately or sequentially with them. Suitable adjuvants include, for example, any substance that enhances the immune response of the subject to the antigen (including when delivered by the polynucleotide of the invention). They may enhance the immune response by affecting any number of pathways, for example, by stabilizing the antigen/MHC complex, by causing more antigen/MHC complex to be present on the cell surface, by enhancing maturation of APCs, or by prolonging the life of APCs (e. g., inhibiting apoptosis).

Examples of adjuvants that may be employed include cytokines. Certain cytokines, for example TRANCE, flt-3L, and CD40L, enhance the immunostimulatory capacity of antigen presenting cells and may be employed. Non-limiting examples of cytokines which may be used alone or in combination include, interleukin-2 (IL-2), stem cell factor (SCF), interleukin 3 (IL-3), interleukin 6 (IL-6), interleukin 12 (IL-12), G-CSF, granulocyte macrophage-colony stimulating factor

(GM-CSF), interleukin-1 alpha (IL-1 a), interleukin-11 (IL-11), MIP-la, leukemia inhibitory factor (LIF), c-kit ligand, thrombopoietin (TPO), CD40 ligand (CD40L), tumor necrosis factor-related activation-induced cytokine (TRANCE) and flt3 ligand (flt-3L). Further examples of adjuvants which may be effective include but are not limited to: aluminium hydroxide, N-acetyl-muramyl-L-threonyl-D-isoglutamine (thr-MDP), N-acetyl-nor-muramyl-L-alanyl-D-isoglutamine (CGP 11637, referred to as nor-MDP), N-acetylmuramyl-L-alanyl-D-isoglutaminyl-L-alanine-2-(1'-2'-dipalmitoyl-sn-glycero-3-hydroxyphosphoryloxy)-ethylamine (CGP 19835A, referred to as MTP-PE), and RIBI, which contains three components extracted from bacteria, monophosphoryl lipid A, trehalose dimycolate and cell wall skeleton (MPL+TDM+CWS) in a 2% squalene/Tween 80 emulsion.

In cases where the invention is used to target a nucleic acid which encodes an antigen to an antigen presenting cell, the nucleic acid may also encode molecules capable of acting as an adjuvant. Thus the nucleic acid may lead to the production of any of the adjuvants mentioned herein and in particular a cytokine or costimulatory molecule. The cytokine may, for example be, IL-1, IL2, and/or IL-12 which will preferably be secreted from the antigen presenting cell. The costimulatory molecule may, for example, be CD80 or CD86 which will be preferably expressed on the cell surface of the antigen presenting cell.

The substances of the invention, and in particular, the vaccines, are typically administered parentally, by injection, for example, either subcutaneously or intramuscularly. Additional possible formulations include suppositories, oral formulations and formulations for transdermal administration. For suppositories, traditional binders and carriers may include, for example, polyalkylene glycols or triglycerides; such suppositories may be formed from mixtures containing the active ingredient in the range of 0.5% to 10%, preferably 1% to 2%. Oral formulations include such normally employed excipients as, for example, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, and the like. These compositions take the form of solutions, suspensions, tablets, pills, capsules, sustained release formulations or powders and contain 10% to 95% of active ingredient, preferably 25% to 70%. Where the substance is lyophilised, the lyophilised material may be reconstituted prior to administration, e.g. a suspension. Reconstitution is preferably effected in buffer.

Capsules, tablets and pills for oral administration to a patient may be provided

with an enteric coating comprising, for example, Eudragit "S", Eudragit "L", cellulose acetate, cellulose acetate phthalate or hydroxypropylmethyl cellulose. Substances of the invention and in particular nucleic acids and vectors of the invention may be administered by needleless injection, for example, transdermally, may also be used.

The substances of the invention may be formulated as neutral or salt forms. Pharmaceutically acceptable salts include the acid addition salt (formed with free amino groups of the peptide) and which are formed with inorganic acids such as, for example, hydrochloric or phosphoric acids, or such organic acids such as acetic, oxalic, tartaric and maleic. Salts formed with the free carboxyl groups may also be derived from inorganic bases such as, for example, sodium, potassium, ammonium, calcium, or ferric hydroxides, and such organic bases as isopropylamine, trimethylamine, 2-ethylamino ethanol, histidine and procaine.

The substances are administered in a manner compatible with the dosage formulation and in such amount will be prophylactically and/or therapeutically effective. The quantity to be administered depends on the subject to be treated, capacity of the subject's immune system to synthesize antibodies, and the degree of protection desired. Precise amounts of active ingredient required to be administered may depend on the judgement of the practitioner and may be peculiar to each subject.

A substance of the invention may be given in a single dose schedule, or preferably in a multiple dose schedule. A multiple does schedule is one in which a primary course of administration may be 1-10 separate doses, followed by other doses given at subsequent time intervals required to maintain and or reinforce the immune response, for example at 1 to 4 months for a second dose, and if needed, a subsequent dose(s) after several months. The dosage regimen will also, at least in part, be determined by the need of the individual and be dependent upon the judgement of the practitioner. Examples of dosages of complex will may be administered include from 5 μg to 100 mg, preferably from 50μg to 50 mg, more preferably from 250μg to 10 mg.

In some cases the administered substances may comprise cells. The cells may, for example, be those comprising nucleic acids or vectors of the invention. In other cases the cells may be loaded antigen presenting cells or may be T cells that have had antigen presented to them by loaded antigen presenting cells of the invention. Any suitable number of cells may be administered to a subject. For example, at least, or about, 10^5, 10^6, 10^7, 10^8, 10^9 cells may be administered. As a guide the number of

cells of the invention to be administered may be from 10^5 to 10^{13}, preferably from 10^7 to 10^{11}. In such cases where cells are administered or present, culture medium may be present to facilitate the survival of the cells. In some cases the cells of the invention may be provided in frozen aliquots and substances such as DMSO may be present to facilitate survival during freezing. Such frozen cells will typically be thawed and then placed in a buffer or medium either for maintenance or for administration.

The nucleotide sequences of the invention and vectors can also be used administered as outlined above. Preferably, the nucleic acid, such as RNA or DNA, in particular DNA, is provided in the form of an expression vector, which may be expressed in the cells of the individual to be treated. The vaccines may comprise naked nucleotide sequences or be in combination with cationic lipids, polymers or targeting systems. The vaccines may be delivered by any available technique. For example, the nucleic acid may be introduced by needle injection, preferably intradermally, subcutaneously or intramuscularly. Alternatively, the nucleic acid may be delivered directly across the skin using a nucleic acid delivery device such as particle-mediated gene delivery. The nucleic acid may be administered topically to the skin, or to mucosal surfaces for example by intranasal, oral, intravaginal or intrarectal administration.

Uptake of nucleic acid constructs may be enhanced by several known transfection techniques, for example those including the use of transfection agents. Examples of these agents includes cationic agents, for example, calcium phosphate and DEAE-Dextran and lipofectants, for example, lipofectam and transfectam. The dosage of the nucleic acid to be administered can be altered. Typically the nucleic acid is administered in the range of 1pg to 1mg, preferably to 1pg to 10μg nucleic acid for particle mediated gene delivery and 10μg to 1mg for other routes.

The following Examples illustrate the invention.

Examples

Example 1

Methods

Recombinant protein expression and purification

Recombinant N-terminal histidine tagged SSL7 and SSL9 proteins from *S. aureus* strain NCTC6571 were produced in *E. coli* using the expression vector pQE30 containing the genes NCTC6571*ssl7* and NCTC6571*ssl9* respectively as previously described (Williams,R.J. *et al., Infect. Immun.* 68, 4407-4415 (2000)). Embp32 from *S. epidermidis* was also expressed as a recombinant N-terminal histidine tag fusion protein in *E. coli* and purified as previously described (Williams,R.J. *et al., Infect. Immun.* 70, 6805-6810 (2002)).

Crystallisation

Crystals of SSL7 were obtained by the hanging drop vapour diffusion technique, at room temperature. Crystals were obtained in two different conditions. For the first condition (form I), the well buffer contained 25-30% (*w/v*) PEG-MME 2K, 0.2 M ammonium sulphate and 0.1 M MES, pH 6.5. Drops consisted of 1 μl recombinant SSL7 at 10 mg/ml and 1 μl well buffer. Crystals had a flat plate morphology with dimensions up to $0.3x0.2x0.01mm^3$. The second condition (form II) had the same protein concentration and drop size, but the well buffer in this case consisted of 28% (*w/v*) PEG 2K and 0.1 M Li_2SO_4 buffered with 0.1M Tricine at pH 8.5. In this case the crystals were rod-shaped with approximate dimensions $0.3x0.05x0.05mm^3$.

X-ray Data Collection

Data were collected from cryocooled crystals following immersion in mother liquor containing 30% (v/v) glycerol (as described in Garmen,E. & Schneider,T. Macromolecular Cryocrystallography. *J. Appl. Cryst.* **30**, 211-237 (1997)).

Form I

The data were collected to 2.75Å resolution on line BM14 at the European Synchrotron Radiation Facility (ESRF; Grenoble, France), on a Mar Research ccd detector. The data were indexed and integrated with Mosflm (Leslie, *Joint CCP4 and ESF-EAMCB Newsletter on Protein Crystallography* **26**, (1992)), and scaled and merged using Scala (Evans *et al.,* 97-103. 1997. CCLRC, Daresbury Laboratory. Ref Type: Conference Proceeding) from the CCP4 suite (*Acta Cryst.* **D50**, 760-763 (1994)). Subsequent analysis was carried out using programs from the CCP4 suite, unless otherwise stated. Data collection statistics are provided in Table 1.

Table 1: Data Collection and Refinement

Res. (Å)	N_{ref} Meas	Uni.	R_{merge}[1] (%) All	High[2]	I/σI All	High	Completeness (%) All	High	Redundancy (%) All	High
Form I ($P4_32_12$)										
45.5-2.75	59980	12607	9.4	46.0	14.6	3.1	98.7	99.2	4.5	4.3
Form II ($P2_12_12_1$)										
30.0-2.7	99169	11049	14.0	48.0	4.6	1.5	99.9	99.9	4.5	3.9

Protein N	[4]B_{ave}(Å^2)	Water N	B_{ave}(Å^2)	R-factor[3] (%) Working[5]	Free[6]	rmsd Bonds(Å)	Angles (°)
Form I ($P4_32_12$)							
3127	43.6	18	30.9	23.5	27.5	0.008	1.35
Form II ($P2_12_12_1$)							
	42.6	24	42.5	23.4	29.9	0.011	1.3

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[1] $R_{merge} = \sum |I_I - I_M| / \sum I_M$, where I_I is the observed intensity of a reflection and I_M is the mean intensity of all related reflections.

[2] High: highest resolution shell. Form I: 2.9-2.75Å; Form II: 2.85-2.70 Å.

[3] $R - factor = \sum |F_{obs} - F_{calc}| / \sum F_{obs}$.

[4] Mean B-factor

[5] For the 95.1% of data included in the refinement.

[6] For the 4.9% of data randomly selected and excluded from refinment.

Autoindexing indicated that the crystals belonged to pointgroup P422, with cell dimensions a=b=81.66 Å, c=148.04 Å and a Matthews coefficient of 3.1 (corresponding to a solvent content of 60% *v/v*) for 2 molecules in the asymmetric unit. There was a significant peak in the native Patterson map at fractional coordinates: 0.000, 0.372, 0.500 and no peaks attributable to non-crystallographic symmetry in the self-rotation function, indicating the presence of two molecules related by a 2-fold rotation parallel to the a-axis in the asymmetric unit.

Form II

The data were collected to 2.7 Å resolution on line ID14-1 at the ESRF, on an ADSC Quantum 4R ccd detector. Data indexing, integration, scaling and analysis was carried out as for form I. Autoindexing and analysis of systematic absences indicated spacegroup $P2_12_12_1$, with a=51.65 Å, b=71.59 Å, c=103.47 Å, and a Matthews' coefficient of 2.00, corresponding to a solvent content of 40%. There was a peak on the self-rotation function at κ=180°, confirming the presence of two molecules in the asymmetric unit. Data collection statistics are provided in Table 1.

Molecular Replacement

The co-ordinates for one monomer of SSL9 (pdb-id: 1M4V; Arcus *et al., J. Biol. Chem.* **277**, 32274-32281 (2002)) were used for molecular replacement, which was carried out with Molrep (Vagin & Teplyakov, *J. Appl. Cryst.* **30**, 1022-1025 (1997)).

Form I

There was a single clear peak in the rotation function ($I/\sigma I$=5.3, next peak $I/\sigma I$=3.58). Since very few systematic absences were recorded during data collection, molecular replacement was carried out in all nine possible spacegroups to unambiguously identify screw axes. The best solution was for spacegroup $P4_32_12$, for which two molecules could be placed in the asymmetric unit, related by the appropriate translation, with a correlation coefficient of 32.6% (for comparison, the best solution in $P4_12_12$ had a correlation coefficient of 26.4%). Sidechains that differed between the SSL5 and SSL7 proteins were replaced by alanines in the

correctly positioned model, and rigid-body refinement was carried out using CNS version 1.1 (Brunger *et al., Acta Cryst.* **D54**, 905-921 (1998)). At this point, the R-factor was 52.2% and the R_{free}, 54.6%. A round of simulated annealing reduced the R- and R_{free}-factors to 44.6 and 48.9% respectively.

Form II

Molecular replacement was performed as described for form I. The best solution had a correlation coefficient of 37.4% for two molecules in the asymmetric unit. Following rigid-body and simulated annealing refinement in CNS, the R-factor and R_{free} were 34.16 and 42.06% respectively.

Density Modification

For both crystal forms, cross-crystal averaging, non-crystallographic averaging and phase improvement were carried out using Dmmulti (Cowtan, *CCP4 Newsletter on Protein Crystallography* (1994)) in CCP4 (*Acta Cryst.* **D50**, 760-763 (1994)), prior to calculation of maps for manual rebuilding of the model.

Model Building and Refinement

In both cases, manual rebuilding was performed using O (Jones & Kjelgaard, Methods in Enzymology. Charles W.Carter,J. & Sweet,R.M. (eds.), pp. 173-208 (Academic Press,1997), and in later refinement rounds XtalView (McRee, Practical Protein Crystallography. Academic Press, San Diego, CA (1993)). Refinement was carried out with CNS. Alanine residues in the initial model were exchanged for the correct sidechains where positive Fourier difference density could be seen. At a number of positions the sequence alignment was incorrect and additional rebuilding of the chain was required. For the refinement, an overall anisotropic B-factor correction and bulk solvent scaling with k=0.36, B=26.9 Å^2, for form I, and k=0.59, B=101 Å^2 for form II were applied. Noncrystallographic symmetry restraints were applied throughout refinement except in the later stages where there was clear evidence of a difference between the chains. After all protein residues had been included in refinement, a number of tightly bound waters were added, where there was a 3 rms peak in the difference Fourier, and a 1 rms peak in the $2F_o$-F_c map, and

appropriate protein-water hydrogen bonds. At the end of refinement, the R-factor was 23.5% and R_{free}, 27.5%, for form I and R=23.4% and R_{free}=29.9% for form II. A homology model of SSL9 was created using the program MODELLER (Lawkowski *et al., J. Appl. Cryst* **26**, 283-291 (1993)) and both SSL7 and SSL5 as template structures.

Structural illustrations were drawn with Bobscript, ((Esnouf, *Acta Cryst.* **D55**, 938-940 (1999)) a modification of molscript (Kraulis, *J. Appl. Cryst.* **24**, 946-950 (1991) and rendered with Raster 3D (Merritt & Bacon, *Methods in Enzymology* **277**, 505-524 (1997) and Bacon & Anderson, *Journal of Molecular Graphics* **6**, 219-220 (1988)).

FITC labelling of SSLs

SSL7 and SSL9 were dialysed against labelling buffer (0.2 M $NaHCO_3$, pH 9.0) overnight at room temperature (RT). 50 µl of 1 mg/ml fluorescein isothiocyanate (FITC, Sigma) in dimethyl sulfoxide (DMSO) was added to 1 ml of a 2 mg/ml protein solution. After 4 hours incubation at room temperature in the dark, unbound FITC was removed by size exclusion chromatography using a PD-10 (Sephadex™) column. The concentration of labelled protein, and the FITC:protein ratio were determined by spectrophotometry. All preparations gave FITC:protein ratios of between 1:1 and 2:1.

Antibodies

The following monoclonal antibodies (MAbs) were used: CD2 (mouse MAb MAS 593, IgG_{2b}; Harlan), CD3 (supernatant mouse MAb UCHT1, IgG_1; obtained from P. C. L. Beverley [Edward Jenner Institute for Vaccine Research, Compton, UK]), CD14 (supernatant mouse MAb HB246, IgG_{2b}; gift from P. C. L. Beverley), and CD19 (supernatant mouse MAb BU12, IgG_1; gift from D. Hardie [Birmingham University, Birmingham, UK]).

Cell culture

Human PBMC-derived dendritic cells (DC) were generated from fresh whole blood samples obtained from healthy volunteers (Alderman *et al., Cardiovasc. Res.*

55, 806-819 (2002) and Newton *et al., Clin. Exp. Immunol.* 133, 50-58 (2003)). Mononuclear cells separated on Lymphoprep ™ (Nycomed Pharma) by centrifugation at 400 *g* for 30 minutes were incubated in six-well tissue culture plates for 2 h at 37°C in 5% CO_2 in complete medium (CM)(RPMI 1640 medium (Gibco) supplemented with 10% fetal calf serum (FCS; PAA Laboratories), 100 U/ml penicillin, 100 μg/ml streptomycin, and 2 mM L-glutamine (Clare Hall Laboratories, Imperial Cancer Research Fund)). The adherent cells were cultured in fresh complete medium with 100 ng/ml human recombinant granulocyte-macrophage colony-stimulating factor (GM-CSF) and 50 ng/ml interleukin (IL)–4 (Schering-Plough Research Institute). On day four of incubation, loosely adherent cells were collected, and contaminating T and B lymphocytes were removed by incubation with CD3, CD2, and CD19 MAbs, followed by anti–mouse IgG–coated immunomagnetic Dynabeads ™ (Dynal). The supernatant, containing highly purified DC was cultured for another three days in fresh complete medium with GM-CSF and IL–4. Human PBMC-derived macrophages were obtained using the same procedure for dendritic cell culture, except that 10% human serum was used and no cytokines were added (Swetman *et al, Eur. J. Immunol.* **32**, 2074-2083 (2002)).

Binding and uptake of FITC labelled SSLs by human cells

Binding assays were performed by incubating 10^6 cells/well in complete medium with various concentrations of SSL-FITC (0.05-1.25 μM) for 1 hour at 4°C or 37°C. In some experiments, 8 μM of unlabelled SSL was added to the cells together with the labelled protein. After incubation, cells were washed three times by centrifugation, and examined by flow cytometry. In some experiments, cells were additionally stained for various surface markers after SSL uptake. Cells were incubated with the relevant MAb for 30 min at 4°C, washed, and then incubated in 1: 25-diluted phycoerythrein-conjugated goat anti–mouse immunoglobulin (PE, Jackson ImmunoResearch) for 30 min at 4°C. Cells were washed, fixed in 2% formaldehyde and examined using a FACScan flow cytometer (Becton Dickinson).

Confocal microscopy

10^5 cells were seeded on 32mm coverslips coated (for dendritic cells only) overnight at $4^{O}C$ with 10μg/ml fibronectin (FN, Sigma) in HBSS (Gibco). After 2 hours at $37^{O}C$ in complete medium, cells were incubated with SSL-FITC (1.25 μM) and/or Texas Red-dextran (1mg/ml, Molecular Probes) for 1 hour at $37^{O}C$ in complete medium. The coverslips were then washed three times in cold HBSS and fixed in 2% paraformaldehyde. The slides were examined on a Bio-Rad Confocal Microscope. Images were acquired from 0.5-μm optical sections of individual cells.

Results

Structure determination of SSL

Recombinant SSL7, consisting of residues 36-231 of the sequence with accession number AF094826 in GenBank, was crystallised in two different conditions each of which gave rise to a different crystal form.

Form I

The final, 2.75Å resolution, model built into the electron density map contained two SSL7 molecules, representing residues 18-213 of the recombinant SSL7. In addition, eighteen water molecules were included at stereochemically sensible locations. Though the His-Tag and N-terminal tail were disordered and omitted from the density, the majority of the residues had well-defined electron density. The final R-factor and R_{free} were 23.5% and 27.5% respectively, and refinement statistics are given in Table 1. The final model had good stereochemistry, with 98.6% of residues in the most favoured and additionally allowed regions of the Ramachandran plot, and no residues in disallowed regions. The geometry was better than expected for the average 2.75 Å structure according to PROCHECK analyses (Lawkowski *et al., J. Appl. Cryst* **26**, 283-291 (1993)).

Form II

This model again contained two SSL7 molecules: in this case residues 21-213 or 23-213 of the construct in chains A and B respectively. Twenty-four water

molecules were added in this form. Once again, with the exception of the His-tag and N-terminal tail, the majority of the molecule had well-defined electron density. The final R- and R_{free}-factors were 23.4 and 29.9% respectively. The final model had good stereochemistry with 96.5% of the residues in the two most favoured regions of the Ramachandran plot. The geometry was better than expected for the average 2.7 Å structure according to PROCHECK. Refinement statistics for both crystal forms are provided in Table 1.

The SSL7 structure

The structure of the SSL7 monomer is shown in Figure 1(a). As predicted from sequence comparisons, the fold is similar to that of the bacterial superantigens, and consists of two domains. The N-terminal domain (residues 18-110) is an OB-fold, a variety of β-barrel associated with oligosaccharide and DNA binding, while the C-terminal domain (111-213) forms a β-grasp domain: a series of β-strands wrapped around a helix.

In total, the structure of four copies of the SSL7 monomer was obtained (two from each crystal form), and they are all very similar, as can be seen from the Cα-atom root mean square deviations (rmsds; Table 2).

Table 2: Root Mean Square deviations (Å) between the different copies of the SSL7 monomer.

		Form I		Form II	
		A	B	A	B
Form I	A	-	0.228	0.701	0.703
	B	-	-	0.669	0.642
Form II	A	-	-	-	0.450
	B	-	-	-	-

The only differences between the structures arise from differences in the conformations of flexible loops, and the linker between the N- and C-terminal

domain (residues 106-112). The relative orientation of the two domains to one another, and the orientations of the individual secondary structural elements remain unchanged in the different copies of the monomer. For this reason, unless explicitly stated, one example monomer, chain A from form I, will be used in the comparisons and discussions that follow.

SSL7 and other proteins

When the SSL7 monomer is superposed on the structure of SSL7 (SET3) (the structure of SSL5 is provided by Arcus *et al., J. Biol. Chem.* **277**, 32274-32281 (2002)), the other member of the family for which a three dimensional structure is available, the two are seen to share the same fold (Figure 1 (b)), as might be expected for proteins sharing 40% sequence identity. However, when optimally superposed, the rmsd, which is 1.33Å over 157 spatially equivalent Cα atoms, is surprisingly high for two such highly related proteins (a value of about 1.1 Å over the whole structure would be anticipated from sequence identity (Chothia & Lesk, *EMBO J.* **5**, 823-6 (1986)).

The high rmsd can be largely accounted for by changes in two regions of the structure. Firstly, there is a change in the twist of the β-sheet in the C-terminal β-grasp domain (Figure 1, (b) right hand structure-indicated by arrow). The change in the twist results in shifts in individual residue positions as large as 6.65 Å (for the Cα atom of G125 in the C-terminal domain). Secondly, there are changes to the conformations of the loops on the external face of the N-terminal OB-fold (Figure 1 (b), left hand structure- indicated by arrow), these loops are associated with a generic low affinity MHCII binding site in superantigens (Jardetzky *et al., Nature* **368**, 711-8 (1994) and Kim *et* al., Science **266**, 1870-1874 (1994)), and changes in them may indicate differences in function between the two proteins. These large movements account for the low contrast and large R-factor for the initial molecular replacement solution, prior to the simulated annealing which successfully realigned the sheet strands, and some of the loop residues.

The SSL7 structure was also compared to a homology model of SSL9, based on both SSL7 and SSL5 as template structures (not shown). The sequence of SSL9 has a much greater homology to SSL7 (sequence identity 49%) than SSL5 (sequence

identity 35%). This is reflected in the model of SSL9: when the structures are optimally superposed SSL9 has a Cα atom rmsd of 0.6 Å over 188 spatially equivalent atoms from SSL7, and 1.4 Å over 177 spatially equivalent atoms from SSL5.

When SSL7, and the superantigen of known structure with which it shares the highest sequence identity (streptococcal pyrogenic exotoxin, SPEC; 29% - Roussel., *Nat. Struct. Biol.* 4, 635-43 (1997)) are optimally superposed (Figure 3), it is seen that once again the overall fold is conserved. SPEC has some extended loops, but the structures are otherwise very similar. Interestingly, despite the SPEC and SSL7 sequences being far more divergent than SSL7 and SSL5, the two structures superpose nearly as well. The Cα atom rmsd for optimally superposed SSL7 and SPEC is 1.48 Å over 134 structurally equivalent atoms. The difference between the structures on this occasion being both a slight change in the orientation of the β-grasp domain (Figure 1, (c) right hand structure, indicated by arrow), but also large differences in the orientations of the strands of the OB-fold (Figure 1, (c), left hand structure-indicated by arrow) the very large changes in conformation in this domain are not unexpected since the SSL proteins do not bind MHC II, and this is the region primarily involved in this interaction in the superantigens.

Dimerisation

In both crystal form I and II there are two molecules in the crystallographic asymmetric unit; these two molecules are related by a proper two-fold, resulting in the formation of an intimate dimer (Figure 1(d)). The dimer is virtually identical in both crystal forms, as can be seen from a comparison of the residues buried in the dimer interface (Figure 2), and the fact that the form I and form II dimers can be superposed with an all Cα atom rmsd of 0.881 Å or 0.902 Å depending on orientation. The remainder of the crystal packing is entirely different for each of the forms, since the crystals grew in different conditions and at markedly different pH; it is unlikely that the dimers formed solely as a result of crystal packing forces.

As can be seen from Figure 1(d) the dimer interface is the result of the two β-grasp domains interacting to create an intermolecular β-sandwich. In the process, 1122 $Å^2$ of the monomer surface in form one and 1146 $Å^2$ of this surface in form II

are buried: this is in the range seen in biologically relevant dimers (Jones & Thornton, *Progress in Biophysics and Molecular Biology* **63**, 31-59 (1995)) . The dimer formation results in the burial of a number of hydrophobic residues (including F119, L128, I132) and a number of neutral polar residues contribute to a hydrogen bonding network between the two monomers, however, no charge-charge interactions are created. It has been shown that protein-protein interaction surfaces differ little from the 'normal' exterior surface of proteins, but that they tend to contain additional neutral polar residues and fewer charged ones (Lo Conte & Janin, *J. Mol. Biol.* **285**, 2177-98 (1999)): the SSL7 dimer interface is entirely consistent with this. Figure 1 (d) also indicated with an arrow the loop with the largest difference between SSL7 and SSL5, the movement of which prevents steric clashes between the two SSL7 molecules in the dimer.

Cellular tropism of SSL7 and SSL9

Peripheral blood mononuclear cells (PBMC) were incubated with various concentrations of SSL7-FITC or SSL9-FITC for 1 hour, and cell-associated fluorescence measured by flow cytometry. Both SSL7 (Figure 3(a)) and SSL9 (not shown) stained a small proportion of PBMC at 37°C, but not at 4 ^{O}C. The level of fluorescence was dose-dependent up to a maximum at 1.25 μM protein. The mean percentage of cells stained with SSL7 (9.8±1.8, range 7.1-12.2, n=7) and SSL9 (10.9±1.1, range 9.4-12.6, n=5) was very similar. Mean fluorescence also increased with time between five minutes and a hundred and twenty minutes (not shown) suggesting progressive uptake of SSL protein by the cells.

In order to determine whether the interaction between SSL protein and PBMC was specific, competitive inhibition of SSL-FITC cell labelling by unlabelled SSL was investigated (Figure 3(b)). Excess unlabelled SSL7 was able to completely block uptake of SSL7-FITC. In contrast, neither SSL9, nor an unrelated bacterial protein also carrying a polyhistidine tag (Embp32) had any effect on the SSL7-FITC signal. Conversely, only unlabelled SSL9, but not SSL7 or Embp32, blocked uptake of SSL9-FITC. Interaction between SSL proteins and the PBMC therefore occurs via a saturable specific receptor, and is not mediated by the histidine tag on these

proteins. Furthermore, SSL7 and SSL9 use different receptors, or different sites within one receptor.

The PBMC sub-populations which are the targets for SSL7 and SSL9 were further characterised by immunophenotyping, using monoclonal antibodies to the major surface markers CD2, CD3, CD14, and CD19 (Figure 4). Both SSL7 and SSL9 were taken up by all CD14 positive cells, and by a population of CD2-low cells, a phenotype consistent with that of peripheral blood monocytes (Crawford,K. *et al., J. Immunol.* **163**, 5920-5928 (1999)). Neither SSL7 nor SSL9 showed any interaction with CD3 positive T cells. Interestingly, SSL7-FITC but not SSL9-FITC stained a subpopulation of CD19 B cells, providing further evidence that the receptor for these two SSLs is distinct.

Uptake of SSLs by dendritic cells

Peripheral blood monocytes were cultured *in vitro* in the presence of GM-CSF and IL-4, in order to drive their differentiation into myeloid dendritic cells ((Sallusto & Lanzavecchia, *J. Exp. Med.* **179**, 1109-1118 (1994)). After depletion of residual lymphocytes, the population obtained after seven days culture consisted of >90% CD1a+ HLA-DR high CD14 low dendritic cells (data not shown).

These cells were incubated for sixty minutes at 37°C with either SSL7-FITC or SSL9-FITC and examined by flow cytometry Figure 5 and confocal microscopy (data not shown). Dendritic cells stained uniformly strongly positive for both SSL7 and SSL9. Confocal microscopy confirmed that fluorescence was predominantly due to intracellular uptake of SSL, rather than surface staining. Both SSL7 and SSL9 were concentrated in small vesicular structures, localised particularly to the perinuclear region of the cell. In order to characterise the nature of these vesicles further, dendritic cells were cultured in the presence of SSL7 or SSL9-FITC and Texas Red dextran (data not shown), which is avidly taken up by dendritic cells via mannose receptors (Sallusto *et al., J. Exp. Med.* **182**, 389-400 (1995)). Texas Red dextran strongly labelled a large number of intracellular vesicles throughout the dendritic cell cytoplasm. SSL distribution and dextran distribution partially overlapped, with some intracellular vesicles clearly containing both markers. However, SSL positive dextran negative vesicles were also observed. In a small

proportion of cells, vesicles containing SSL9 appeared to aggregate, to generate very large vesicles, which contained high concentrations of both SSL and dextran. The very large vesicles observed (which were never seen in the presence of dextran alone) presumably resulted from fusion of many SSL containing vesicles, and may have been driven by intramolecular interactions between SSL molecules (as observed during dimerisation in crystal structure). Similar vesicle distortion is observed in the presence of excess invariant chain, again driven by multiple interactions between invariant chain molecules (Romagnoli *et al.*, *J. Exp. Med.* 177, 583-596 (1993).

In order to determine whether uptake of SSLs was a generalised feature of endocytic cells, peripheral blood monocytes were differentiated into macrophages, via culture in human serum, without added cytokines. Under these culture conditions, the cells develop a completely different phenotype (CD1a-,HLA-DR-,CD14 high) and morphology (lack of dendrite formation) (Swetman *et al, Eur. J. Immunol.* **32**, 2074-2083 (2002). Macrophages, like dendritic cells efficiently endocytosed Texas Red dextran, but showed no uptake of either SSL7 or SSL9 (data not shown).

Discussion

One of the most exciting results from the structural studies of SSL7 was the identification of an identical SSL7 homodimer in the asymmetric unit of two otherwise very different crystal forms, grown from very different solution conditions. The dimer has a number of characteristics seen in functionally relevant dimers, and which indicates that the dimer is not purely an artefact of crystallization. Interestingly, the structure of SSL5 did not reveal any such dimer formation (Arcus *et al., J. Biol. Chem.* **277**, 32274-32281 (2002) and the residues making up the interface are not conserved across the different SSL proteins.

The change in the orientation of the β-grasp domain in SSL7 relative to SSL5 is necessary to allow the dimer to form: if a similar dimer is created from SSL5 monomers, clashes occur between residues 110-114 in one monomer and 197-200 in the other, and more seriously between residues 118-125 and 161-165. These clashes are alleviated by the change in the orientation of the β-grasp domain β-strands in SSL7, further suggesting that SSL7 does not form a dimer in the same way.

Since no crystal structure of SSL9 is yet available, a preliminary comparison with SSL7 was carried out using a homology model. As for SSL5, the residues involved in the dimer interface in SSL7 are not conserved between SSL7 and SSL9. However the sequence changes do not create steric or electrostatic clashes between the two monomers; rather they are such that hydrogen-bonding between the two molecules is maintained, and in some cases, new hydrogen-bonds are formed. SSL9 may therefore form a dimer in the same manner as SSL7.

SSL7 and SSL5 show differences in the region of the N-terminal domain that are implicated in a general low-affinity MHCII binding site in superantigens. The homology model reveals that the residues in these loops are in general highly conserved between the SSL7 and SSL9 sequences. However there are some important differences, including the change of P93 in SSL7 to threonine in SSL9. This proline is part of a well ordered β-turn in SSL7, while in SSL5 there is no ordered secondary structural element present here: in fact this in SSL5 loop is rather disordered. The pattern of sequence conservation in the N-terminal loops indicates that the structures of SSL7 and SSL9 are more related to one another than to SSL5 and this may also be reflected in the functional properties of the molecules. However, the small number non-conservative sequence changes between SSL7 and SSL9 are also entirely consistent with differences in their putative receptor binding, as discussed further below.

Studies of the superantigens have shown that their interactions with MHCII and T cell receptor molecules are diverse, encompassing a number of different interaction surfaces and stoichiometries. This includes the formation of functionally important superantigen dimers for some superantigens, for example the Zn^{2+}-dependent dimers formed by staphylococcal exotoxin D (Sundstrom *et al.*, *EMBO J.* **15**, 6832-40 (1996)), which form via the C-terminal β-grasp domain, in a manner reminiscent of the homodimers seen of SSL7. It also includes the formation of heterodimers using the same surface of the N-terminal OB-fold but different surfaces of MHC molecules (as in the complexes of HLA-DR1 with SEB and TSST-1 respectively - Jardetzky *et al., Nature* 368, 711-8 (1994) and Kim *et* al., Science 266, 1870-1874 (1994)).

The functional and structural studies described here show that SSL7 and SSL7, may be functionally active in different quaternary states.

The most significant differences between the structures of SSL7, SSL5 and other superantigens suggest that these molecules may interact with different binding partners, and this is supported by the studies of cellular tropism. The characteristic features of the interaction between SSL7 and SSL9, and PBMC are specificity, temperature dependence and cell selectivity. Specificity, indicative that the interaction is mediated by a cell surface receptor, is shown by the demonstration that unlabelled SSL blocks uptake of SSL-FITC. This competition is observed for both SSL7 and SSL9, ruling out the hypothesis that the results are due to significant differences in affinity of binding between the two.

The lack of reciprocal inhibition between SSL7 and SSL9 indicates that these two molecules have different binding partners on the cell surface, although the possibility that they bind to different sites on the same molecule cannot be ruled out. Although the binding sites of SSL9 and 5 on the cell surface are distinct, both are able to self-target to APCs. Since it was impossible to measure binding in the absence of uptake, true measurements of affinity could not be obtained. The concentrations required to obtain measurable uptake, however, were in the order of 0.1 micromolar, suggesting that the affinity of interaction with any putative receptor is relatively low. This is a characteristic of many classical superantigens (Labrecque *et al., Semin. Immunol.* **5**, 23-32 (1993)).

The temperature and time dependence of SSL interaction are suggestive of receptor mediated uptake rather than simple binding to the cell surface, and this was confirmed by the confocal microscopy studies discussed further below. However, a small amount of surface binding can be detected at 37°C, but not 4°, using indirect labelling of intact cells with an antibody against the histidine tag (not shown). The interaction of SSL with the receptor, as well as its subsequent uptake, is therefore temperature-dependent.

The third characteristic of SSLs observed in these cellular studies with PBMC was the highly selective nature of the target population with which interaction could be detected. In *ex vivo* PBMC, the major target population is the monocyte, characterised by high expression of CD14. Essentially all monocytes were found to

interact with both SSL7 and SSL9. In contrast, neither SSL7 nor SSL9 interacted with T cells, identified by expression of CD3 and high levels of CD2. Interestingly, SSL7, but not SSL9 also bound to a proportion of B cells (in the order of 30% although this varied significantly between individuals), providing further evidence that the receptor for these two molecules is distinct. Since a very significant proportion of T cells, and all human B cells also express class II MHC (e.g. HLA-DR) this result rules out a direct binding of SSL7 or SSL9 to these molecules, thus clearly distinguishing them from classical superantigens.

Monocytes express both class I and class II MHC molecules, and can act as antigen presenting cells for the activation of CD4 or CD8 T cells. However, the prototype antigen presenting cell, and the only cell type which can activate naïve T cells, is the dendritic cell. It was therefore of interest that both SSL7 and SSL9 were taken up efficiently by monocyte-derived dendritic cell and hence both molecules can self target to this important class of antigen presenting cells. This cell type, which can be obtained by culture of PB monocytes in appropriate cytokines, provides a widely used model for myeloid dendritic cells. In contrast, neither SSL7 nor SSL9 showed any tropism for macrophages, a cell type also produced by *in vitro* culture of monocytes, but which has no antigen presenting capabilities.

Studies indicate that antigen presenting cell activity remains intact in the presence of SSLs. Conversely, self-targeting to antigen presenting cells results in enhancing the immunogenicity of these proteins. The uptake of SSL7 and SSL9 into an endosomal compartment which intersects with the dextran uptake pathway indicates that the SSL7 are successfully targeted to the antigen presentation pathway. This is because uptake via the mannose receptor efficiently targets antigens to the Class II MHC antigen processing pathway (Sallusto *et al., J. Exp. Med.* **182**, 389-400 (1995)). Although enhancing immunogenicity would, at first sight, appear to be paradoxical, the generation of an antibody response to a secreted protein is unlikely to confer any advantage in bacterial clearance by the host. On the contrary, the interaction between secreted toxin and specific antibody in the microenvironment of the bacterium may activate complement and hence contribute to the breakdown of the physical barriers that restricts the invasiveness of these bacteria.

SSLs therefore appear to provide *S. aureus* with an alternative molecular strategy with which to distract the protective adaptive immune response of the host, and contribute to bacterial pathogenicity. Specifically, SSLs achieve this through their ability to target antigen presenting cells.

Example 2

The work described in Example 1 shows SSLs (*staphylococcal* superantigen like proteins) interact selectively with antigen presenting cells, including dendritic cells. The functional consequences of this interaction are now examined further. We show that SSL uptake does not adversely effect any of the parameters of antigen presenting cell function examined using dendritic cells. SSL7 and 9 were found to have no effect on viability or morphology of dendritic cells. The proteins did not induce dendritic cell maturation, as measured by cell surface phenotype. Exposure to SSL did not alter the ability of dendritic cells to take up FITC-dextran. In addition, exposure to SSLs did not impair the ability of the dendritic cells to stimulate allogeneic or antigen specific T-cell responses.

The ability of antigen presenting cells to present SSLs was also examined. Dendritic cells loaded with SSL7 or 9 were able to stimulate a T-cell proliferative response in three out of eight healthy individuals tested. Sera from nine out of ten individuals tested contained antibodies against both SSL7 and SSL9, and the response to each SSL was specific and not cross-reactive.

The results obtained demonstrate that SSLs can be used to specifically target antigen presenting cells and gain access to the antigen presentation pathway of these cells. SSLs may therefore be utilised to specifically deliver chosen antigens to antigen presenting cells in order to elicit an immune response against the chosen antigen.

Methods

Recombinant protein expression and purification

Recombinant N-terminal histidine tagged SSL7 and SSL9 proteins from *S. aureus* strain NCTC6571 and Embp32 from *S. epidermidis* were produced as described above in Example 1. SSL proteins without histidine tag behaved identically to the tagged version in terms of cell binding and uptake (Al Shangiti AM *et al.*, Infect. Immun., 72:4261-70 (2004).

Antibodies

The following monoclonal antibodies (MAbs) were used: CD2 (mouse MAb MAS 593, IgG_{2b}; Harlan), CD3 (supernatant mouse MAb UCHT1, IgG_1; gift from P. C. L. Beverley [Edward Jenner Institute for Vaccine Research, Compton, UK]), CD14 (supernatant mouse MAb HB246, IgG_{2b}; gift from P. C. L. Beverley), and CD19 (supernatant mouse MAb BU12, IgG_1; gift from D. Hardie [Birmingham University, Birmingham, UK]), HLA-DR (supernatant mouse MAb L243, IgG_{2a}; gift from P. C. L. Beverley), HLA-ABC (W6/32; Serotec), CD86 (supernatant mouse MAb BU63, IgG1; gift from D. Hardie), and CD54 (Mouse IgG MEM-111, gift from Prof. Horejsi, Academy of Science, Prague, Czech Republic). Fluorescein isothiocyanate (FITC) conjugated anti-mouse rabbit polyclonal antibody was purchased from Dako. PE-conjugated anti-CD1a (Monoclonal Mouse IgG1, clone BL6, Immunotech, Marseille, France). The rabbit polyclonal antibody to His-SSL7 was produced under contract by Eurogentec Ltd (Southampton, UK) and validated by Western blot and ELISA.

Dendritic Cell Preparation

Monocyte-derived human dendritic cells (MDDC) were generated from fresh whole blood samples obtained from healthy volunteers as described previously (Al Shangiti *et al.*, (2004), *supra*). Briefly, mononuclear cells separated on Lymphoprep™ (Nycomed Pharma) by centrifugation at 400g for 30 mins were incubated in 6-well tissue culture plates at 37°C in 5% CO_2 in complete medium (CM)(RPMI 1640 medium (Gibco) supplemented with 10% fetal calf serum (FCS; PAA Laboratories), 100 U/ml penicillin, 100 µg/ml streptomycin, 2 mM L-glutamine (Clare Hall Laboratories, Imperial Cancer Research Fund), 100 ng/ml human

recombinant granulocyte-marcrophage colony-stimulating factor (GM-CSF) and 50 ng/ml interleukin (IL)-4 (Schering-Plough Research Institute). On day four of incubation, loosely adherent cells were collected, and contaminating T and B lymphocytes were removed by incubation with CD3, CD2, and CD19 MAbs, followed by anti-mouse IgG-coated immunomagnetic Dynabeads™ (Dynal). The non-adherent fraction, containing highly purified dendritic cells (less than 5% CD3, CD19 or CD14) was cultured for another three days in fresh culture medium with GM-CSF and IL-4.

Cell viability

10^5 dendritic cells/group were cultured with SSL7 or SSL9 (4.16 µM) in a 96-well plate, and the plate was incubated at 37°C in 5% CO_2 overnight. Cell viability was assessed by trypan blue exclusion assay. 10 µl of cells suspension were diluted in an equal volume of trypan blue solution. 10 µl of this mix were loaded on a haemocytometer counting chamber placed under the microscope and white live cells (dead cells turn blue) were counted with in a 4 x 4 square grid.

Cell surface phenotype expression

Dendritic cell surface staining was performed by using a panel of monoclonal antibodies (MAbs) directed against surface antigens expressed by dendritic cells and the appropriate specific isotype controls. Briefly, 10^5 cells were pre-incubated for 24 hours in culture medium with 4.16 µM of SSL7 or SSL9 or with PG (5 µg/ml, from S. aureus, Sigma) or purified LPS (100 ng/ml; Salmonella Minnesota, Sigma) in 96 well U-bottomed plates at 37°C. Cells were resuspended in 100 µl of staining buffer (HBSS, 1% FBS, 0.1% sodium azide), and incubated first with the relevant MAbs for 30 mins at 4°C. Cells were washed, and secondary immunolabeling was performed using FITC-conjugated rabbit anti-mouse immunoglobulin (30 min, 4°C). Cells were washed three times and fixed in 3.8% paraformaldehyde and examined within 5 days on a FACScan flow cytometer (Becton Dickinson). Data were analysed using CellQuest software.

Endocytosis assay

Dendritic cells (10^5) were incubated in culture medium with or with 4.16 µM of SSL7 or SSL9 for various times (1 or 18 hours) in 96 well U-bottomed plates at 37°C. Different concentrations (1, 3, 10 and 30 µg/ml) of FITC-dextram (40,000 MW) were incubated with the cells. After 1 hour of incubation at 37°C, cells were washed in ice cold HBSS containing 0.1% azide to stop further endocytosis, fixed with 3.7% formaldehyde, and analysed by flow cytometry. The uptake of dextran is expressed as mean fluorescent intensity. For each sample at least 5000 events gated on dendritic cells were analysed.

T-cell Proliferation Assays

Autologous T-cells were obtained from non-adherent population of peripheral blood mononuclear cell fraction from eight healthy volunteers (age range 20-50, median approximately 30) and Cryopreserved in FCS containing 10% DMSO (Sigma Aldrich) at -70°C. Cells were thawed rapidly (37°C), and B cells, monocytes, and macrophages were depleted by incubation with CD19, HLA-DR and CD14 MoAb for 45 minutes on ice. Cells were washed and then mixed with magnetic microbeads and separated on magnetic columns. T-cells (greater than 90% purity) were used immediately after purification. Allogeneic T-cells used in mixed leucocyte reactions (MLR) were prepared from HLA-mismatched donors in same procedure. Purified dendritic cells (10^4), either untreated or treated for 18 hours to different concentration of SSL proteins (4.16, 1.25 and 0.42 µM), were incubated at 37°C/5% CO_2 with autologous T-cells (2 x 10^5 cells/well) in the presence of purified protein derivative (PPD) or with allogeneic T-cells in flat-bottomed 96-well microtiter plates. The dendritic cell autologous and allogeneic T-cell cocultures were incubated 6 days. Both assays were then pulsed with 1 µCi of [^{3}H]thymidine (ICN Biomedical, High Wycombe, United Kingdom) for the final 18 hours of culture. Cells were harvested, and T-cell proliferation was measured by liquid scintillation counting (Microbeta Systems). All assays were performed in triplicate. Results were express as cpm. Error bars represent the standard deviation (SD).

Cytokines assays

Autologous T and dendritic cells were incubated with different concentrations of SSL proteins (4.16, 1.25 and 0.42 µM) at 37°C/5% CO_2 in 24-well plates. After 4 days, cell culture supernatants were centrifuged for the removal of cells and stored at -70°C. Cytokine detection was done by enzyme-linked immunosorbent assay (ELISA) for interleukin-10 (IL-10, Pharmingen, UK), gamma interferon (IFN-γ, Pharmingen, UK) and IL-13 (ImmunoTools, Germany). Purified protein derivative (PPD; 500 U/ml) was used as positive control.

Antibody detection

Human serum was collected from heparinised blood of ten normal individuals (three females, seven males, age range 20-50, median 30). ELISA miscroassay plates were coated for 24 hours with 0.04 µM of SSL proteins dissolved in sodium carbonate buffer 0.1 M, pH = 9.5 at 4°C (100 µl/well). After three successive washes with HBSS containing 0.1% Tween 20™, blocking was performed with 1% skimmed milk in HBSS for 1 hour at 37°C. The plates were washed again three times, as before, and the tested sera diluted at 1:2000 in HBSS with 0.1% Tween™ were added to the SSL coated plates for 1 hour at 37°C (preliminary studies showed that this diluation of antisera gave no background staining for any serum tested in control wells). After three additional washes, the remaining bound antibodies were incubated for 1 hour at 37°C with alkaline phosphates – conjugated human antibodies diluated at 1:1000 in HBSS with 0.1% Tween 20™. Excess conjugate was removed by washing as above and a colorimetric reaction was carried out by addition of the chromogen OPD (o-Phenylenediamine dihydrochloride) for 15-20 minutes. The plates were read (405 nm) to detect the optical density (OD) readings. A control well containing no serum was used to detect the background count. A polyclonal rabbit antibody raised against purified His-tagged SSL was included as a positive control (anti-SSL7).

Competitive ELISA was performed by mixing the sera with differing concentrations of SSL or a control bacterial protein Embp32 (0.08, 0.17, 0.33 and 0.42 µM), and then testing binding on SSL-coated plates as above.

Statistical analysis

The means of paired groups were analysed by a 2-tailed Student's t test. The level of significance was <0.05.

Results

The effects of SSL protein on DC viability, morphology and surface phenotype

Monocyte-derived dendritic cells (MDDC) were derived from peripheral blood monocytes. They showed the characteristic phenotype with low CD14, and high HLA-DR and high CD1a. As shown in Figure 1, fluoresceinated SSL7 and SSL9 labelled CD1a expressing cells dendritic cells in unpurified dendritic cell cultures, while residual contaminating cells (predominantly lymphocytes) did not show any interaction with either protein. Nevertheless, in order to exclude the possibility of indirect effects mediated on dendritic cells via some other cell type all further experiments were performed on purified dendritic cell cultures, containing less than 5% non-dendritic cells.

Dendritic cells were incubated with SSL7 or SSL9 (4.16 µM) for either 1 or 18 hours at 37°C and cell viability was assessed by trypan blue exclusion. Microscopic analysis revealed that SSL proteins were not cytotoxic as more than 95% of cells appeared viable. Untreated cells were predominantly non-adherent with few dendritic cell processes, typical of immature dendritic cells (Figure 7A, top panel). Neither SSL7 or SSL9 induced any noticeable morphological changes over the time period tested (Figure 7A, middle panels). In contrast dendritic cells treated with the TLR4 bacterial ligand LPS (100 ng/ml) or peptidoglycan (PG) 5 µg/ml) became adherent and extended multiple, long dendritic processes (Figure 7A, bottom panels). The cell-surface expression of a panel of characteristic dendritic cell surface markers was analyzed by flow cytometry. Immature dendritic cells were incubated with 4 µM SSL7 or SSL9, or LPS and PG and the surface phenotype of these dendritic cells was analysed after 18 hours of culture. Neither SSL7 or SSL9 (Figure 7B) induced significant changes in any of the surface molecules measured. In contrast, dendritic cells incubated with either LPS or PG up-regulated surface expression of HLA-DR, HLA-ABC, CD86 and CD54. Thus, in summary, exposure

of dendritic cells to the SSLs protein did not induce dendritic cell maturation, nor indeed any obvious changes in dendritic cell surface phenotype, viability or morphology.

The influence of SSLs on endocytosis

Fluorescein isothiocyanate-labelled dextran (FITC-Dx) is rapidly taken up by dendritic cells via the mannose receptor (Sallusto F., *et al.*, J. Exp. Med., 182:389-400 (1995)). To determine whether SSL protein altered antigen uptake function, dendritic cells were treated with 4.16 μM of SSL7 or SSL9 and incubated for 1 or 18 hours at 37°C. Different concentrations of FITC-Dx (1, 3, 10 and 30μg/ml) were added to the cell and incubated for a further hour at 37°C, and FITC-Dx update by the dendritic cell was then measured by flow cytometry. Figure 8 shows the results obtained with the total cell associated dextran being measured by flow cytometry and expressed as mean fluorescent intensity for a minimum of 5000 dendritic cells. As shown in Figure 8, SSL treated dendritic cell showed rapid update of FITC-Dx, and neither protein had any effect on endocytic activity.

The influence of SSLs on the T-cell stimulatory capacity of dendritic cells

To evaluate the effect of SSL proteins on the stimulatory capacity of dendritic cells in T-cell proliferation, day 6 dendritic cells (10^4) were incubated for 18 hours with different concentrations of SSL proteins (0.42, 1.25, and 4.16 μM). Residual T-cells were depleted and the functional assays performed using fresh viable purified autologous or allogeneic T-cells (2×10^5). The ability to induce secondary immune responses was unchanged. Figure 9A shows representative experiments eliciting recall responses to tuberculin (PPD – 500 U/ml)). There was no statistical difference in the proliferative responses observed between any of the pre-incubated dendritic cell groups with SSL 7 or SSL9 (37182 $\pm$ 2036 cpm and 36458 $\pm$ 3000 cpm, respectively) and the control (36458 $\pm$ 6151 cpm) after the 6 days co-culture period (P>0.05).

The capacity of SSL-treated dendritic cells (10^4) to elicit primary T-cell proliferation also was tested in an allogeneic mixed lymphocyte reaction (MLR). The same concentrations of SSL 7 and 9 and number of T cells used in the autologous

assay were emplyed with the allogenic T cells. A similar result was observed (Figure 9B), as proliferation response against allogeneic T-cells (25710 ± 1140 cpm) was unaffected by the treatment of SSL7 or SSL9 (26149 ± 3674 and 25816 ± 3159 cpm, respectively (P>0.05)). Therefore, SSL proteins have no effect on the ability to induce proliferation of allogeneic T-cells. In general, the results of these experiments demonstrate that the antigen presentation capacity of dendritic cells remains intact in the presence of these secreted proteins.

T-cell responses to SSLs in the normal human population

To investigate the ability of SSLs to stimulate a recall T-cell response in healthy volunteers, dendritic cells (10^4) were incubated with autologous T-cells (2 x 10^5) from normal donors in the presence of different concentrations of SSL proteins (0.42, 1.25, and 4.16 μM) for 6 days (Figure 10). Purified protein derivative (PPD) was used as a positive control. A recall response against SSL7 was documented in 2/8 individuals and a response to SSL9 in 3/8 individuals. All volunteers showed a good recall response against PPD (70889 ± 3146 rpm).

The supernatants of three dendritic cell/T-cell/SSL co-cultures (individuals 1, 2 and 8 from Figure 10) were tested for IFN-γ (TH1), IL-13 (TH2) and IL-10 (Treg) after 4 days. All cytokine levels were low (IFNγ < 700pg/ml n=3); IL-13 < 50 pg/ml, n=3) or undetectable (IL-10). The results for the individual with maximum response (individual 1 in Figure 10) at different SSL concentrations are shown in Figure 11.

Antibodies responses to SSLs in the normal human population

In order to see if the presence of a T-cell response correlated with antibody production, sera from ten individuals (including those tested for T-cell responses as shown above) were tested by ELISA against immobilized SSL7 and SSL9 (Figure 12A). Sera was diluted 1:2000 and tested for binding to SSL7 or SSL9 by ELISA as described in the materials and methods section. Nine out of time individuals tested showed antibody responses to both SSL7 and SSL9 at this dilution. Interestingly, competitive ELISA (Figure 12B and C) showed that the antibody response was highly specific for individual SSL isotypes. Increasing concentrations of SSL7

(Figure 12B) were able to completely block the interaction between SSL7 protein and SSL7 sera. In contrast, neither SSL9, nor an unrelated bacterial protein (Embp32) had any effect on the SSL7 antibody binding. Conversely, only SSL9, but not SSL7 or Embp32, were able to block SSL9-antibody (Figure 12C). Therefore, interaction between SSL proteins and SSL-antibodies were specific and do not cross-react.

Discussion

Dendritic cells as professional antigen presenting cells have a key role in the initiation of the immune response against microbial infections; therefore, many microbial strategies have been described which interfere with dendritic cell function (Moll H., Cell Microbiol., 5:493-500 (2003)). One possibility was that SSLs might interfere with normal function of dendritic cells and therefore impair the protective immune response to *S. aureus*. Such functions have recently been proposed for the anthrax lethal toxin (Agrawal A, *et al.*, Nature, 424:329-34 (2003)) and *E. coli* heat labile toxin (Petrovska L, *et al.*, Vaccine, 21:1445-54 (2003)). The possibility of SSLs inhibiting dendritic cell function was therefore ruled out in the present study.

SSL7 or SSL9 were shown to be non-toxic to antigen presenting cells and did not alter the characteristic morphology of these cells (cf the effect of *Clostridium difficile* toxin B, (Swetman CA *et al.*, Eur. J. Immunol., 32:2074-83 (2002)). Conversely, SSL7 and SSL9 did not induce process extension, or up-regulation of cell surface co-stimulatory and HLA molecules on the dendritic cell, two characteristic signs of activation/maturation responses induced by whole *S. aureus* (Tourkova IL, *et al.*, Immunol. Lett., 78:75-82 (2001)) or bacterial surface components such as peptidoglycan (PG) (Michelsen KS, *et al.*, J. Biol. Chem., 276:25680-6 (2001)). Thus, although SSLs bind to and are taken up by dendritic cells (Figure 6) this interaction does not appear to engage activating receptors on the dendritic cell surface. Previous studies (Williams RJ, *et al.*, Infect. Immun., 68:4407-15 (2000)) indicating that SSLs could activate high levels of inflammatory cytokine release from peripheral blood cells could not be repeated using the highly

purified protein preparations used for this study (data not shown) and may have resulted from trace amounts of contaminating LPS.

In addition to their specialized dendritic morphology and cell surface phenotype, dendritic cells are characterized by extremely rapid endocytosis by both fluid phase and receptor mediated update (Swanson JA, *et al.*, Trends Cell Biol., 5:424-8 (1995) and Levine TP, *et al.*, Adv. Exp. Med. Biol. 329:11-5 (1993)). The uptake of FITC-Dextran, which is believed to be mediated via mannose receptors on the cell surface (Sallusto F, *et al.*, J. Exp. Med., 182:389-400 (1995)) is frequently used to measure the latter. Dendritic cells did indeed show efficient internalization of FITC-Dextran (albeit slightly less well after overnight culture) and this uptake was not altered by exposure to SSL7 or SSL9. Finally, since dendritic cells are distinguished by being the most potent stimulators of both primary and secondary T-cell responses, we tested the effects of SSL7 and SSL9 exposure on dendritic cell function directly. Although dendritic cells stimulated powerful proliferative responses to both PPD (a classical recall secondary response to BCG vaccination) and allogeneic purified T-cells (predominantly a primary response) neither SSL7 nor SSL9 altered the antigen presentation activity of dendritic cells. Taken together, therefore, these data do not provide any evidence that SSL proteins inhibit or modify dendritic cell function.

Further experiments demonstrated that SSL targeted to antigen presenting cells, in particular dendritic cells, actually are delivered to the antigen presentation pathway. This can hence enhance an immune response to these proteins and can also be used to deliver chosen antigens to the same pathway. The immune response to SSLs was analysed in a small panel of healthy human volunteers. Although none of the individuals tested had any known history of clinical *S. aureus* infection, the organism is extremely prevalent in the environment and approximately 30-40% individuals are persistently colonized by *S. aureus*, usually in the nasal mucosa (Nair SP, Williams RJ, Henderson B, Advances in our understanding of the bone and joint pathology caused by *Staphylococcus aureus* infection, Rheumatology, (Oxford), 2000; 39:821-34). Indeed, in eight volunteers tested, three (37%) showed a dose dependent T-cell response to dendritic cells loaded with SSL9 and two to SSL7. The response was detectable with relatively large numbers of T-cells/well (2×10^5) and

induced the release of a very low level of either TH1 (IFN-γ) or TH2 (IL-13) cytokines, suggesting precursor frequency of T-cell specific for SSL was likely to be low.

Despite a low T-cell precursor frequency, the humoral response to SSL7 and SSL9 was robust. Using solid phase ELISA nine out of ten sera tested showed specific antibody binding to both SSLs. The response measured was IgG (using an anti-IgG detection antibody) suggesting that class switching had occurred and further implicating the activity of SSL-specific T-cells. Interestingly, some individuals (e.g. individuals 2 and 7 in Figures 10 and 11) show antibody responses, but no detectable T-cells responses, perhaps because precursor T-cell frequency has fall below detectable levels in these individuals. One individual showed a T-cell response to SSL9, but no antibody response to either SSL tested, although we cannot rule out that some antibody might be detectable at a lower dilutions. Interestingly, the antibody response to each SSL was highly specific with minimal evidence of cross-SSL reactivity. This data is consistent with the sequence diversity between SSL paralogs, despite a highly conserved three dimension structure (Al Shangiti *et al* (2004) *Supra* and Arcus VL, *et al.*, J. Biol. Chem., 277:32274-81 (2002)). The presence of SSL specific immunity in so many individuals, and the existence of so many SSL paralogs in the *S. aureus* genome, is suggestive of a strong evolutionary interaction between host immunity and this bacterial family of proteins.

In conclusion, this study describes a number of functional consequences of the interaction between SSL and dendritic cells. In contrast to some other bacterial exotoxins (Agrawal *et al*, (2003), *Supra* and Petrovska *et al.*, (2003) *Supra*) SSLs do not appear to damage dendritic cells, but rather can be taken up by them, and thus stimulate T-cell response in healthy individuals. This means that SSLs may be employed to selectively deliver chosen antigens to antigen presenting cells, in particular to dendritic cells. SSLs may therefore be used to help induce an immune response or tolerance to a selected antigen.

CLAIMS

1. Use of a complex comprising:

(a) a targeting polypeptide comprising a staphylococcal superantigen-like protein (SSL), a fragment thereof or a variant of either, where the SSL, fragment or variant has the ability to target the complex to an antigen presenting cell; and

(b) an antigen and/or a nucleic acid molecule encoding an antigen,

in the manufacture of a medicament for use in immunization or the induction of tolerance.

2. Use according to claim 1, wherein the antigen comprises a polypeptide which is present in the complex as a fusion polypeptide with the targeting polypeptide.

3. Use according to Claim 1 or 2, wherein the antigen and targeting polypeptides are not part of the same polypeptide, but are covalently joined to each other or are joined through a linker.

4. Use according to any one of the preceding claims, wherein the antigen is a pathogenic antigen, an auto-antigen, an allergen and/or a cancer antigen.

5. Use according to any one of the preceding claims, wherein the targeting polypeptide is present as a dimer.

6. Use according to any one of the preceding claims, wherein the targeting polypeptide comprises:

(a) a polypeptide having the amino acid sequence of any of SEQ ID Nos 6, 7, 9, 20, 21, 23, 30, 32, 34, 40, 44, 42, 58, 59, 60 72, 74, and/or76;

(b) a fragment of any of the sequences of (a), the fragment having the ability to target the complex to an antigen presenting cell; and/or

(c) a variant polypeptide having at least 30% amino acid sequence identity

to any of the polypeptides of (a) or (b) and the ability to target the complex to an antigen presenting cell.

7. Use according to claim 6, wherein the targeting polypeptide comprises:

(a) the sequence of SEQ ID No: 7, 9, 21, 23, 32, 34, 40, 42, 59, 60, 74, 76 and/or 92;

(b) a fragment of any of the sequences of (a), the fragment having the ability to target the complex to an antigen presenting cell; and/or

(c) a variant polypeptide having at least 70 % amino acid sequence identity to any of the polypeptides of (a) or (b) and the ability to target the complex to an antigen presenting cell.

8. Use according to any one of the preceding claims wherein the medicament is for the induction of tolerance and is to be administered without an adjuvant.

9 A complex comprising:

(i) a targeting polypeptide as defined in any one of the preceding claims; and

(ii) an antigen or a nucleic acid encoding an antigen, wherein the antigen or encoded antigen is selected from a pathogenic antigen, auto-antigen, an allergen and a cancer antigen.

10. A complex according to claim 9, wherein the targeting polypeptide is present as a dimer.

11 A virus comprising a targeting polypeptide as defined in any one of claims 1 to 8.

12. A nucleic acid molecule comprising a polynucleotide sequence encoding a targeting polypeptide and antigen, wherein the targeting polypeptide and antigen are as defined in claim 9.

13. A nucleic acid according to claim 12, wherein the nucleotide sequence encoding the targeting polypeptide and the antigen are present in a single open reading frame.

14. A vector comprising a nucleic acid according to claim 12 or 13.

15. A vector according to claim 14, comprising a promoter capable of giving rise to expression of both the targeting polypeptide and the antigen in an antigen presenting cell.

16. A cell comprising a nucleic acid according to claim 12 or 13 or a vector according to claim 14 or 15 or infected with a virus according to claim 11.

17. A method of loading antigen presenting cells comprising contacting an antigen presenting cell or a precursor thereof with a complex as defined in any one of claims 1 to 10 or a virus according to claim 11

18. A method according to claim 17, which is an *in vitro* method.

19. An antigen presenting cell which has been loaded with a complex as defined in any one of claims 1 to 10 or a virus according to claim 11.

20. A pharmaceutical composition comprising a complex as defined in any one of claims 1 to 10, a nucleic acid encoding the targeting polypeptide and antigen of a complex as defined in any one of claims 1 to 10, a vector comprising such a nucleic acid, a cell comprising such a nucleic acid or vector, a virus according to claim 11 or an antigen presenting cell according to claim 19 and a pharmaceutically acceptable carrier or diluent.

21. A vaccine comprising a complex as a complex as defined in any one of claims 1 to 10, a nucleic acid encoding the targeting polypeptide and antigen of a complex as defined in any one of claims 1 to 10, a vector comprising such a nucleic

acid, a cell comprising such a nucleic acid or vector, a virus according to claim 11 or an antigen presenting cell according to claim 19.

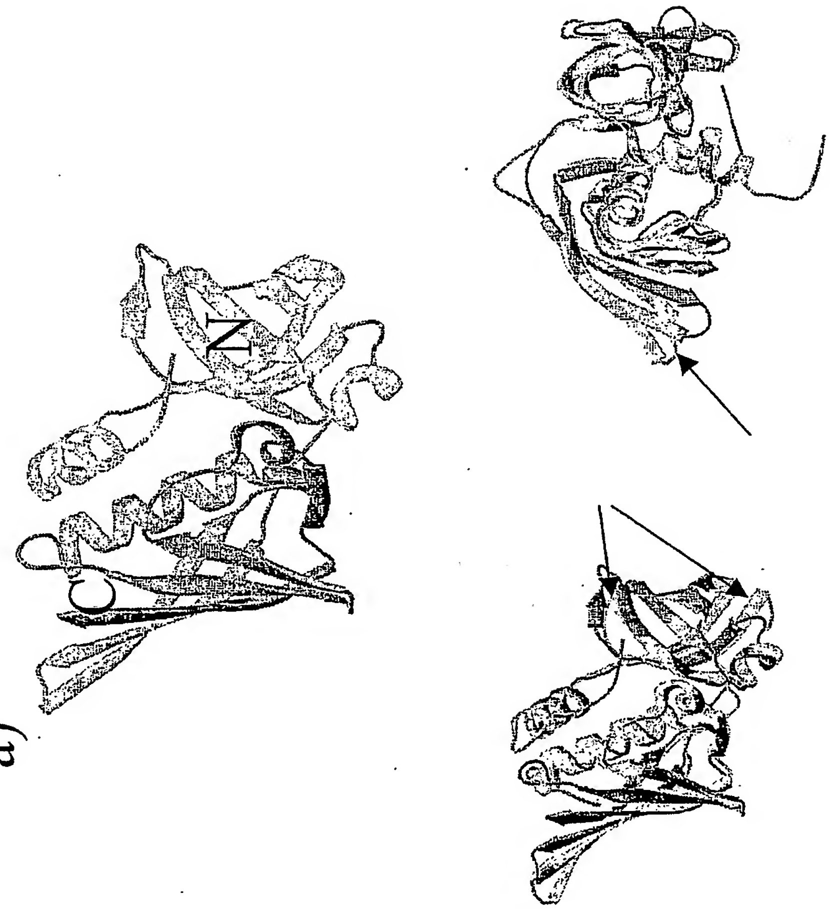
22. A complex as defined in any one of claims 1 to 10, a nucleic acid encoding the targeting polypeptide and antigen of a complex as defined in any one of claims 1 to 10, a vector comprising such a nucleic acid, a cell comprising such a nucleic acid or vector, a virus according to claim 11, or an antigen presenting cell according to claim 19 for use in a method of treatment of the human or animal body by therapy.

23. Use of a nucleic acid encoding the targeting polypeptide and antigen of a complex as defined in any one of claims 1 to 10, a vector comprising such a nucleic acid, a cell comprising such a nucleic acid or vector, a virus according to claim 11 or an antigen presenting cell according to claim 19 in the manufacture of a medicament for use in immunisation.

24. A method of immunising a subject, the method comprising administering an effective amount of a complex as defined in any one of claims 1 to 10, a nucleic acid encoding the targeting polypeptide and antigen of a complex as defined in any one of claims 1 to 10, a vector comprising such a nucleic acid, a cell comprising such a nucleic acid or vector, a virus according to claim 11 or an antigen presenting cell according to claim 18 to a subject.

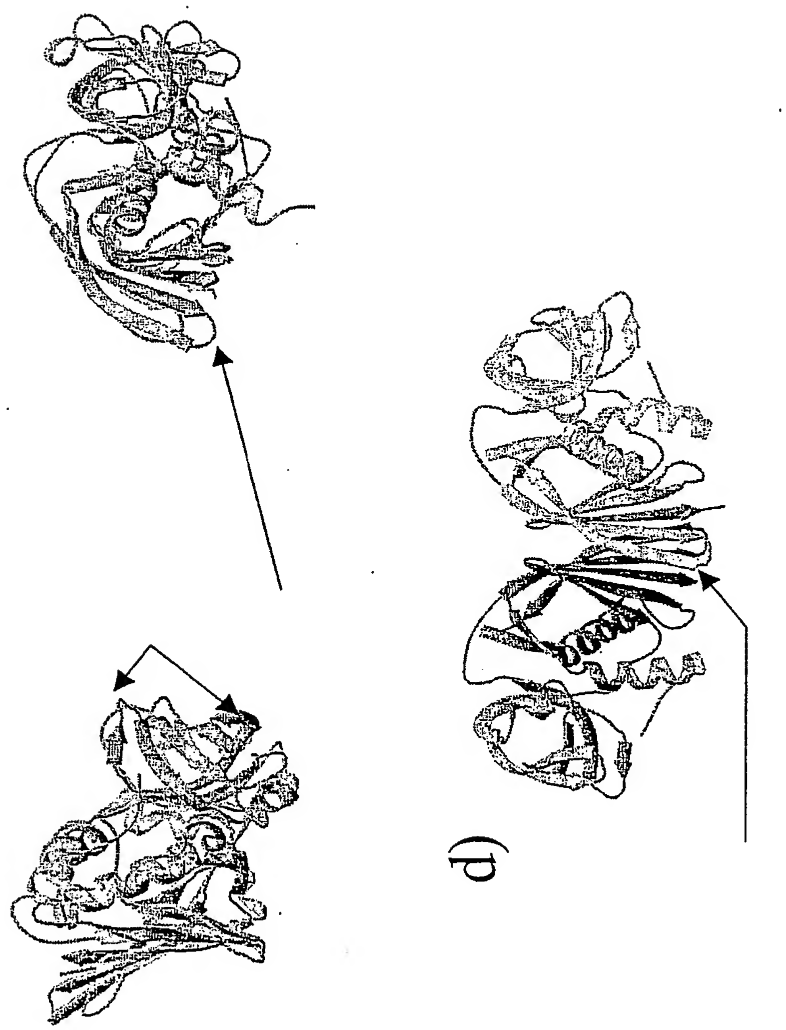
25. An agent for immunising a subject, the agent comprising a complex as defined in any one of claims 1 to 9, a nucleic acid encoding the targeting polypeptide and antigen of a complex as defined in any one of claims 1 to 9, a vector comprising such a nucleic acid, a cell comprising such a nucleic acid or vector, or an antigen presenting cell according to claim 17.

a)



b)

Figure 1



c)

d)

Figure 1 (continued)

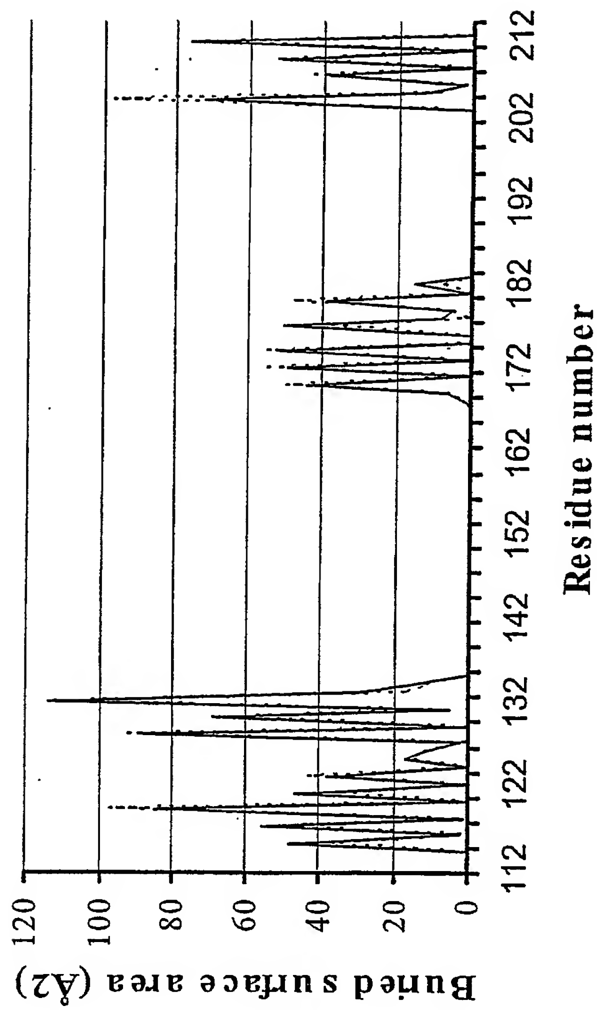

Buried surface area (Å2)
120
100
80
60
40
20
0
Residue number
112
122
132
142
152
162
172
182
192
202
212

Figure 2

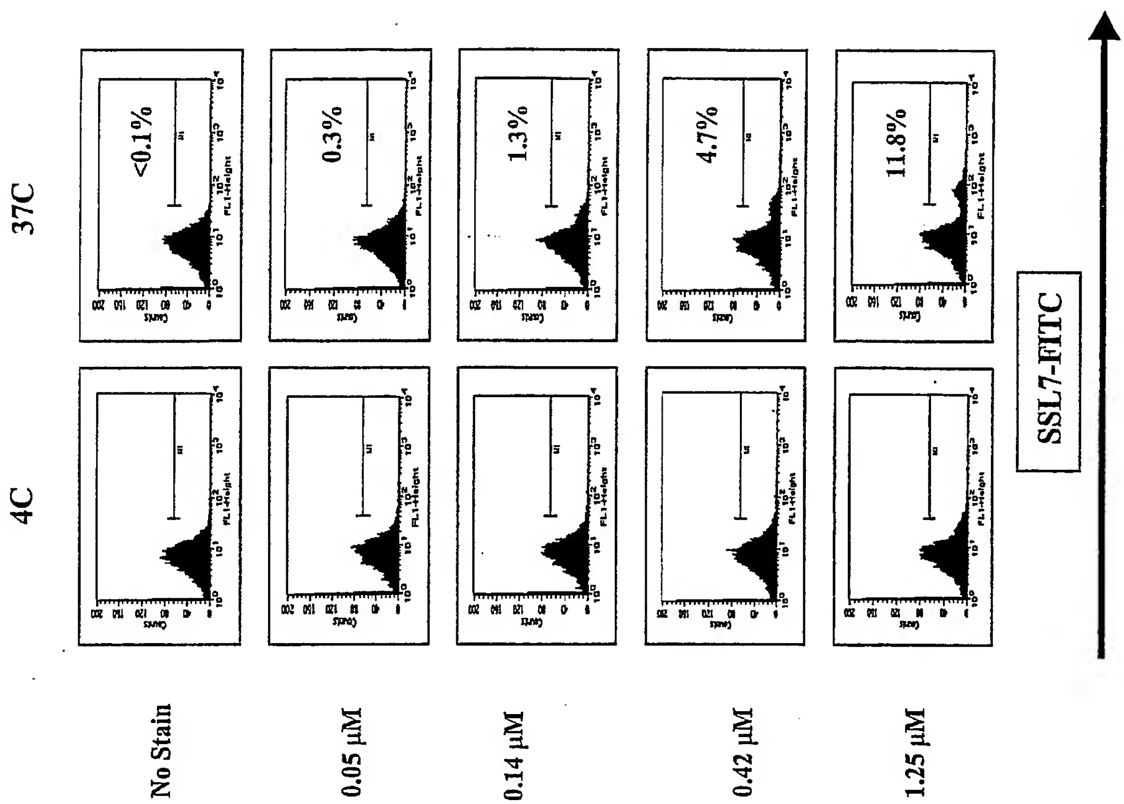

4C
37C
<0.1%
0.3%
1.3%
4.7%
11.8%
SSL7-FITC
No Stain
0.05 µM
0.14 µM
0.42 µM
1.25 µM

Figure 3(a)

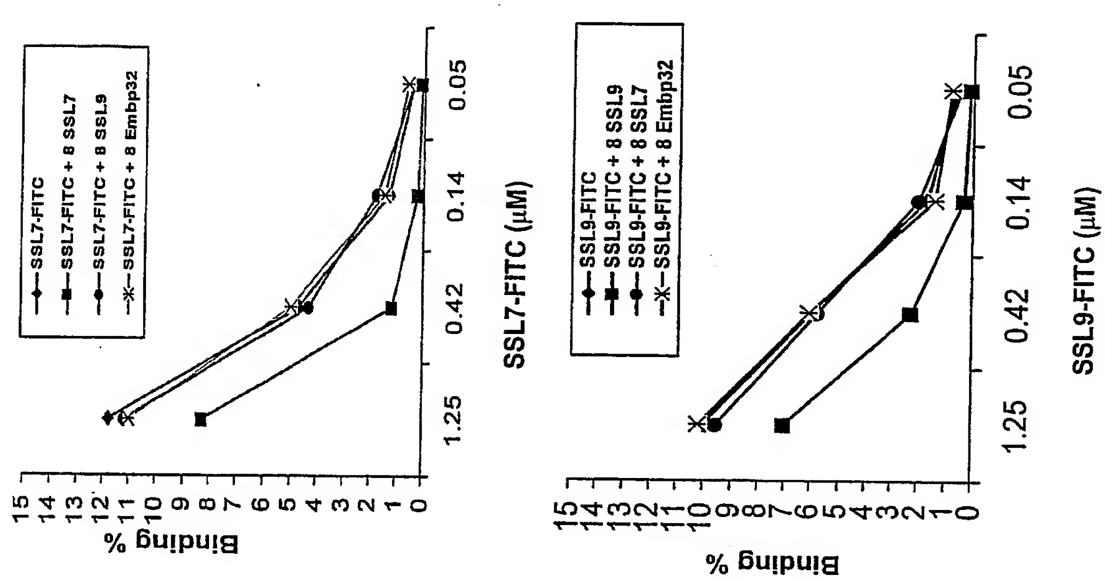

SSL7-FITC
SSL7-FITC + 8 SSL7
SSL7-FITC + 8 SSL9
SSL7-FITC + 8 Embp32
Binding %
SSL7-FITC (μM)
1.25
0.42
0.14
0.05
SSL9-FITC
SSL9-FITC + 8 SSL9
SSL9-FITC + 8 SSL7
SSL9-FITC + 8 Embp32
Binding %
SSL9-FITC (μM)

Figure 3 (b)

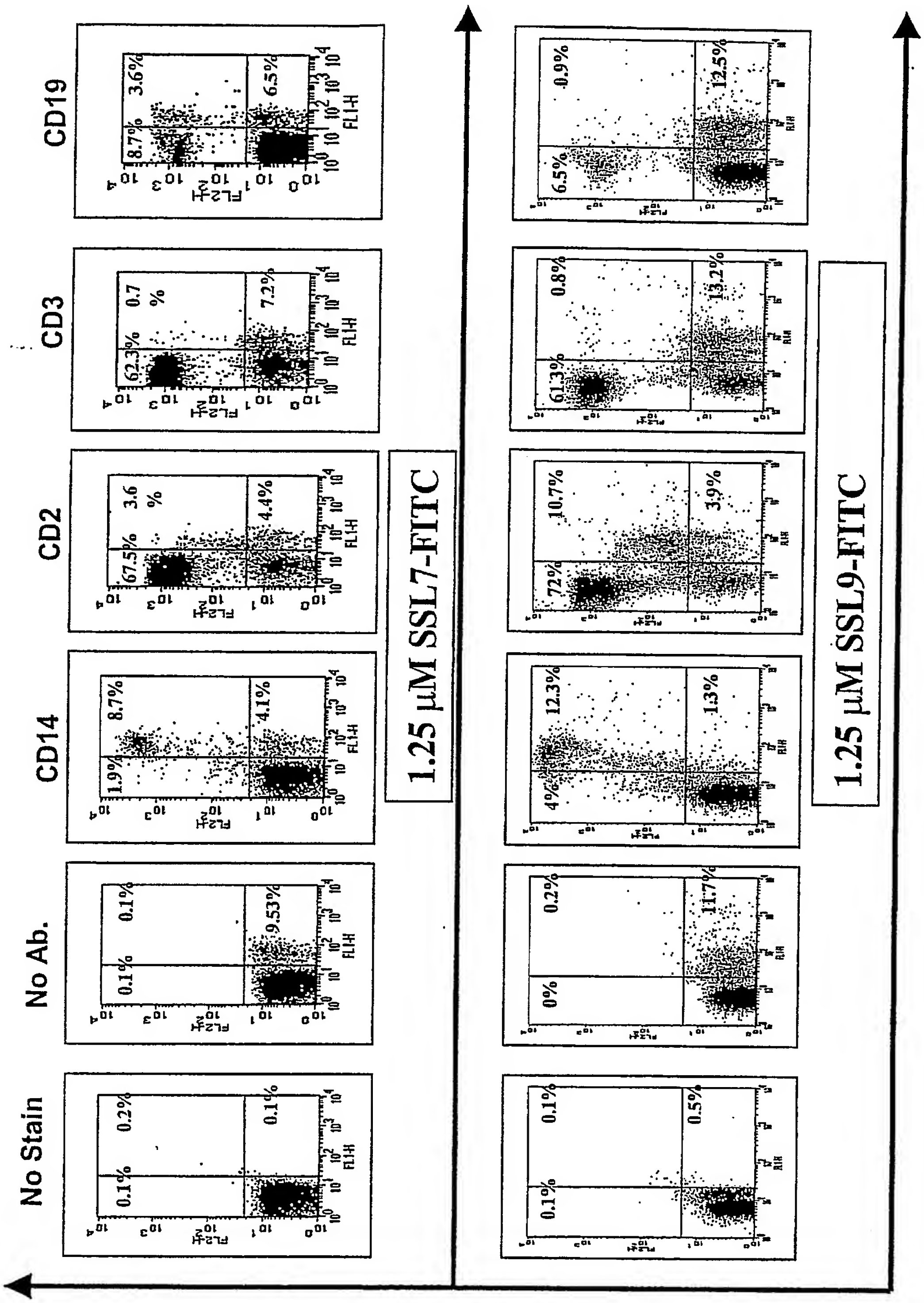

No Stain
No Ab.
CD14
CD2
CD3
CD19
1.25 μM SSL7-FITC
1.25 μM SSL9-FITC

Figure 4

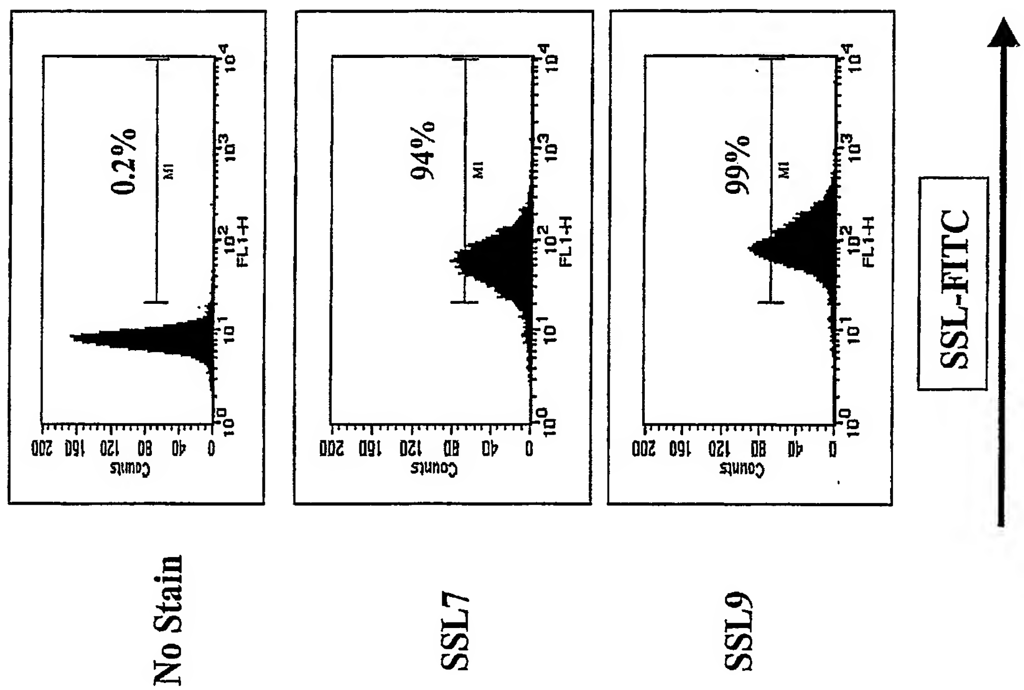


Figure 5

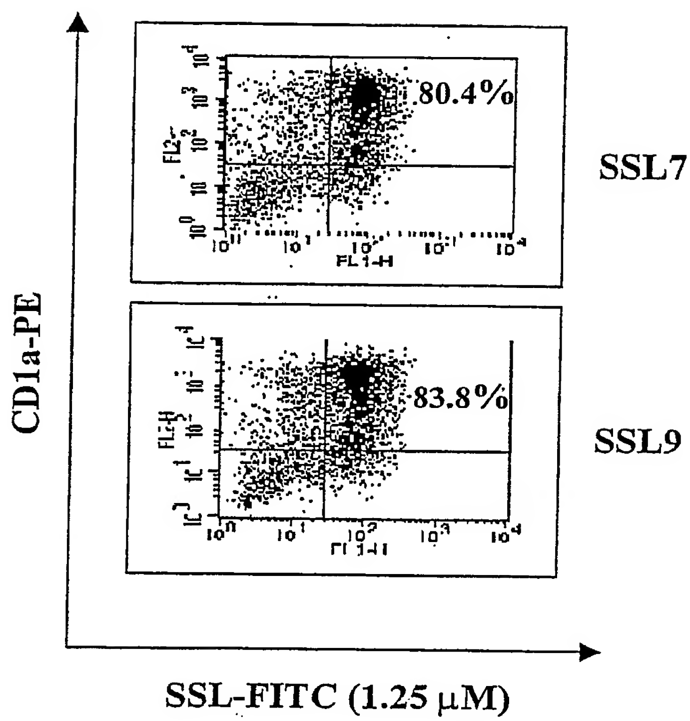


Figure 6

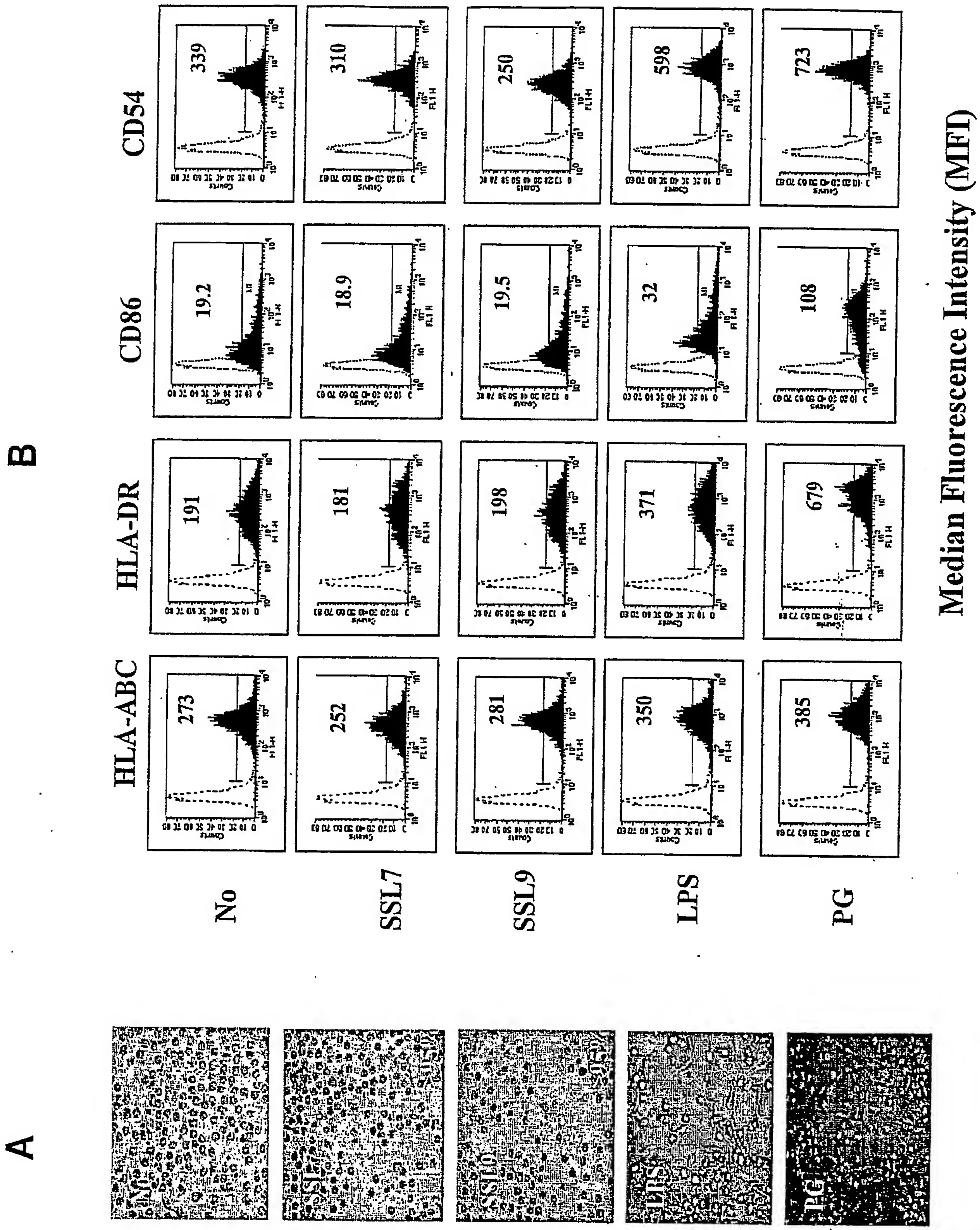

A
B
HLA-ABC
HLA-DR
CD86
CD54
No
SSL7
SSL9
LPS
PG
273
191
19.2
339
252
181
18.9
310
281
198
19.5
250
350
371
32
598
385
679
108
723
Median Fluorescence Intensity (MFI)

Figure 7

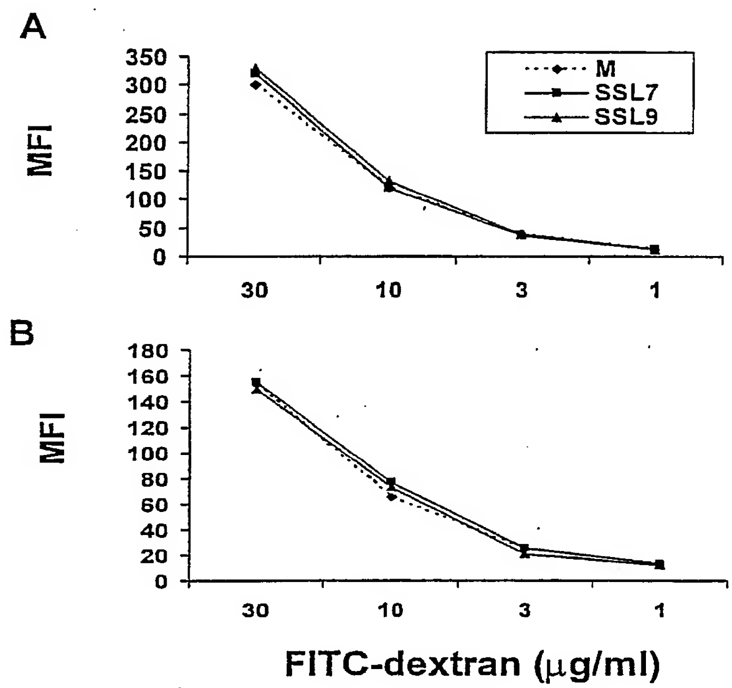

A
MFI
350
300
250
200
150
100
50
0
30
10
3
1
M
SSL7
SSL9
B
MFI
180
160
140
120
100
80
60
40
20
0
30
10
3
1
FITC-dextran (μg/ml)

Figure 8

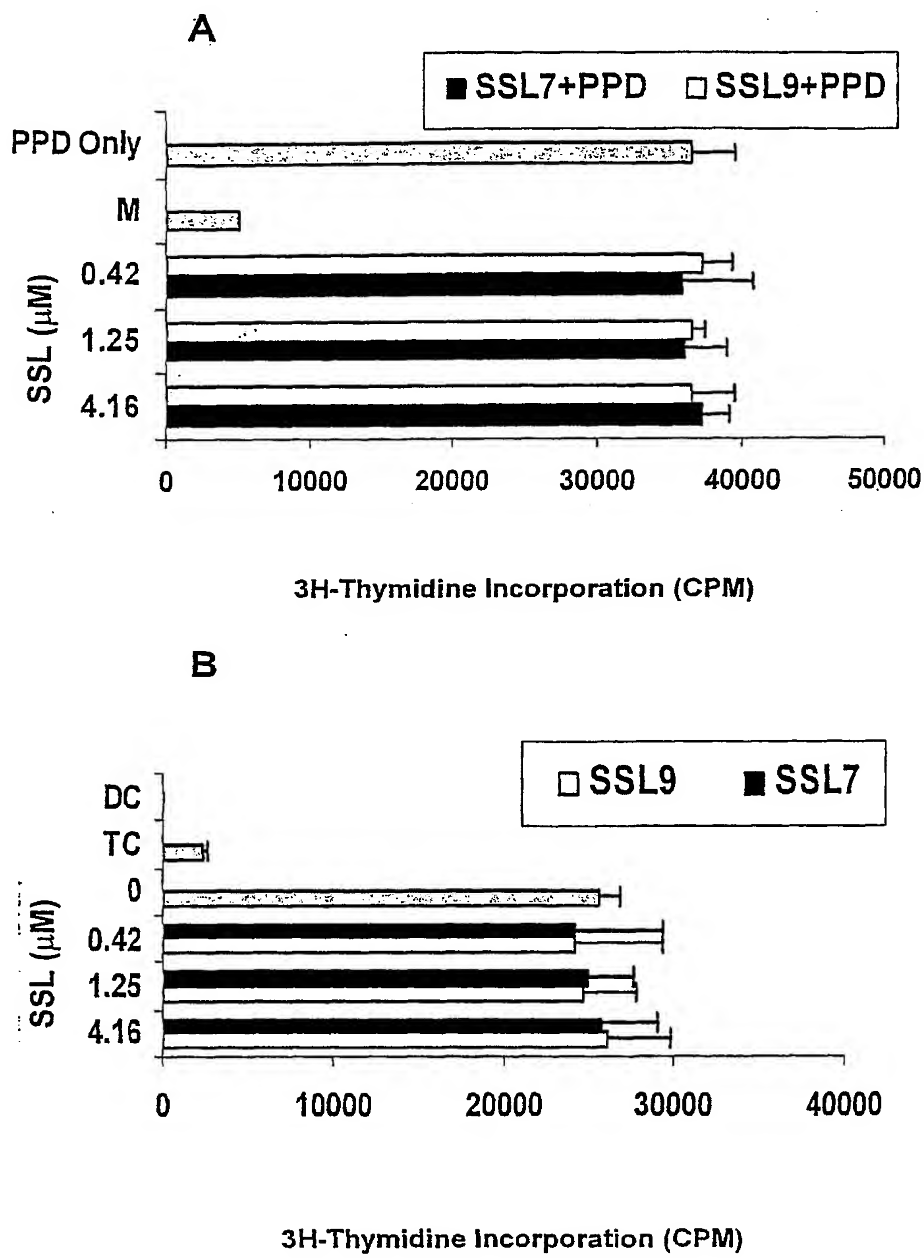

A
SSL7+PPD
SSL9+PPD
PPD Only
M
0.42
1.25
4.16
SSL (μM)
0
10000
20000
30000
40000
50000
3H-Thymidine Incorporation (CPM)
B
SSL9
SSL7
DC
TC
0
0.42
1.25
4.16
SSL (μM)
0
10000
20000
30000
40000
3H-Thymidine Incorporation (CPM)

Figure 9

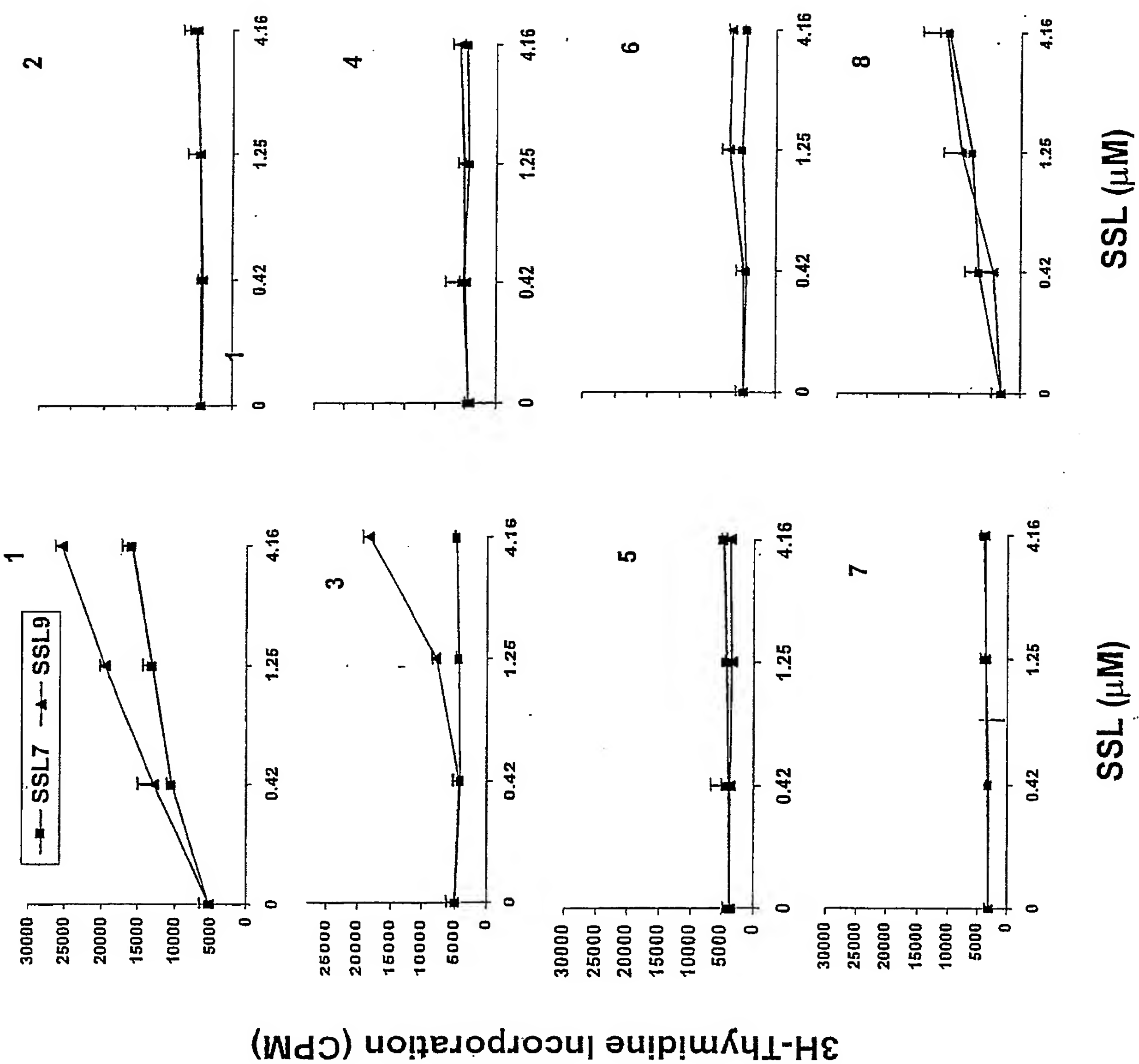

SSL7
SSL9
1
2
3
4
5
6
7
8
0
0.42
1.25
4.16
30000
25000
20000
15000
10000
5000
3H-Thymidine Incorporation (CPM)
SSL (μM)

Figure 10

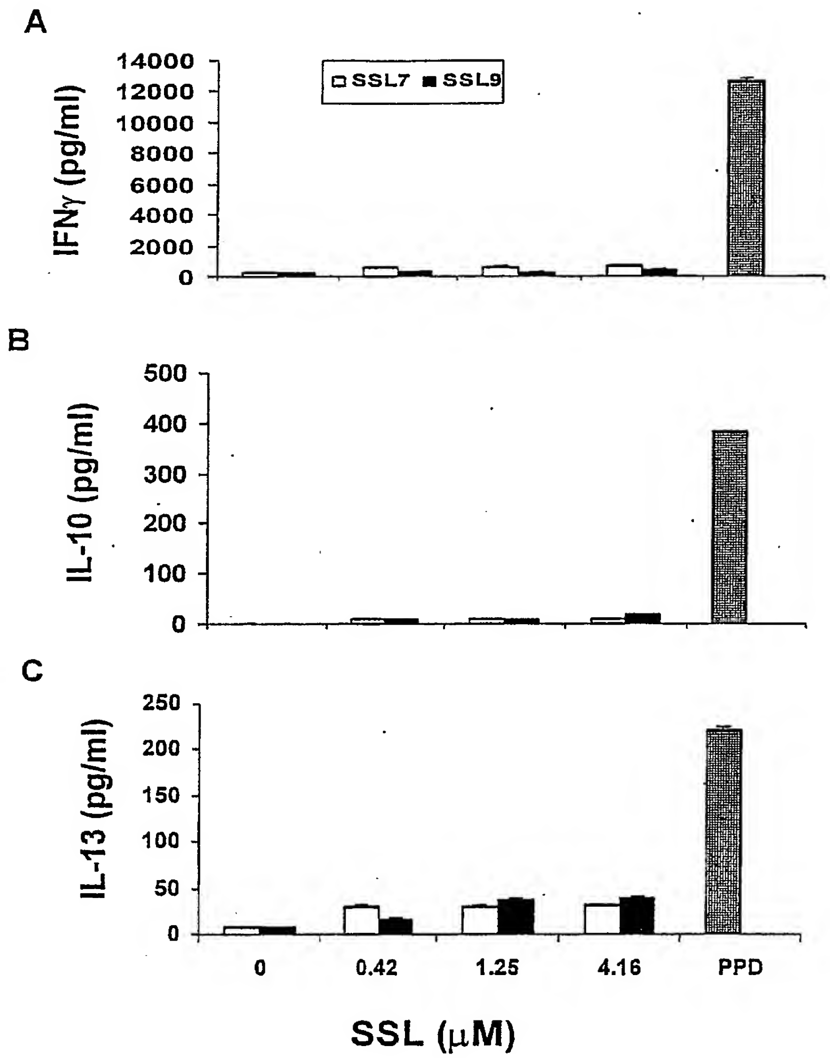

A
14000
12000
10000
8000
6000
4000
2000
0
IFNγ (pg/ml)
SSL7 SSL9
B
500
400
300
200
100
0
IL-10 (pg/ml)
C
250
200
150
100
50
0
IL-13 (pg/ml)
0
0.42
1.25
4.16
PPD
SSL (μM)

Figure 13

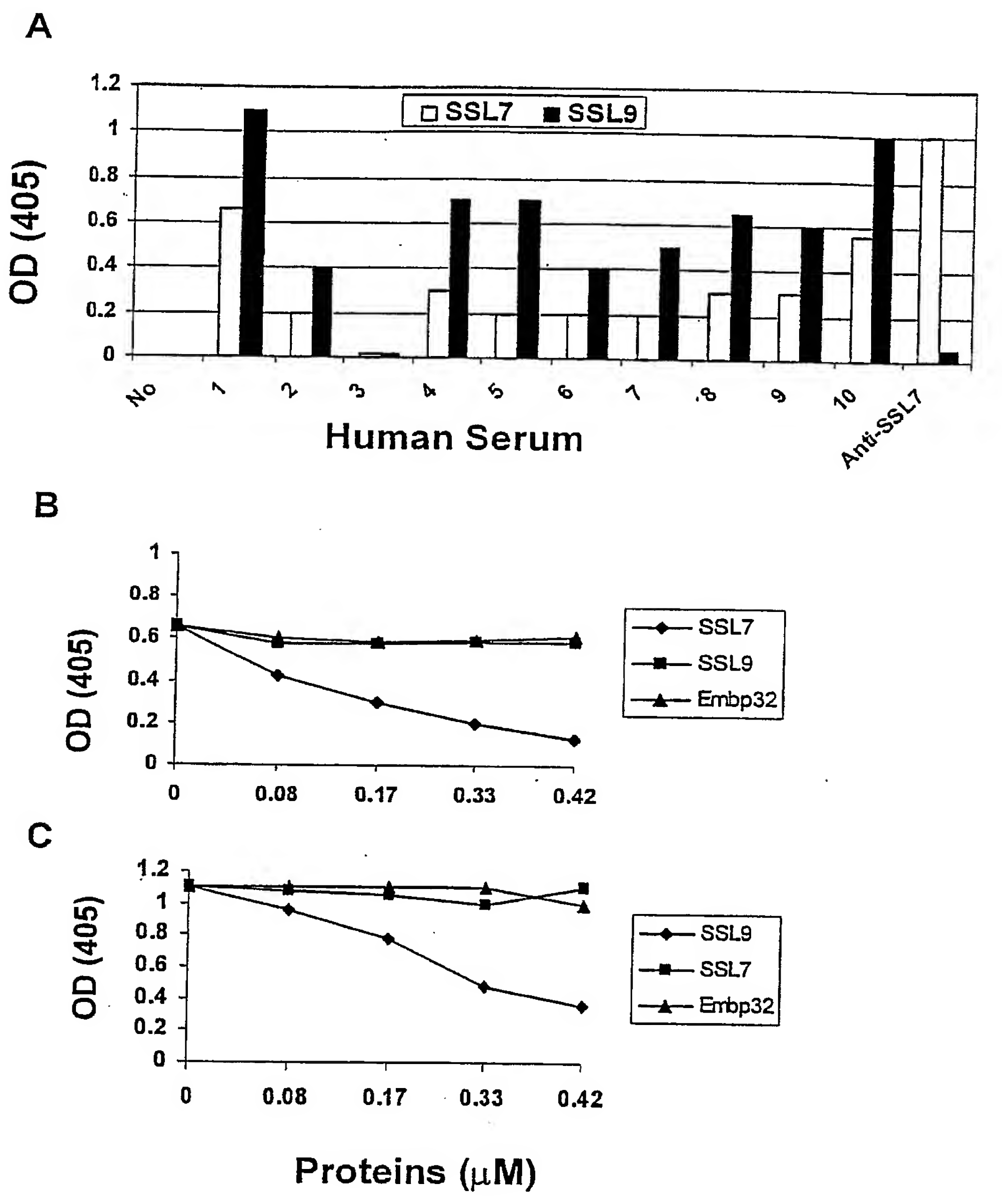

A
1.2
1
0.8
0.6
0.4
0.2
0
OD (405)
SSL7
SSL9
No
1
2
3
4
5
6
7
8
9
10
Anti-SSL7
Human Serum
B
1
0.8
0.6
0.4
0.2
0
OD (405)
0
0.08
0.17
0.33
0.42
SSL7
SSL9
Embp32
C
1.2
1
0.8
0.6
0.4
0.2
0
OD (405)
0
0.08
0.17
0.33
0.42
SSL9
SSL7
Embp32
Proteins (μM)

Figure 14

SEQUENCE LISTING

S. aureus strain N315 taken from GenBank

SEQ ID no:1

```
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143221 agagttgaaa cactattata ataaaccggt tttagagcgt aaaaatgtta ctggatataa
143281 atatactgaa aaaggtaaag attatataga tgttatagta gacaatcaat attctcaaat
143341 ttctttagtt ggatctgata aagacaaatt taaagatgga gacaactcga atatagatgt
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144181 tgaaaatagc aaaaaattaa aagcttatta tactcaacct agtattgaat ataaaaatgt
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144901 tcattatttt ttgcttaaat tacttaataa tacttcaata attgttaaaa agggtttaat
144961 gtgattatct tagaacgcca tctataatga tgttgtatga ttcaaattac gtaaaaagac
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146101 aaaattgaag tgaatataaa ataatcatga cgttctctaa atagaagctg acatcggtaa
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146581 acaccatctt ccactaaagt ggaagcacca caatcaacac cgccctcaac taaagtagaa
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SEQ ID No:9 - SSL9

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SEQ ID No:12

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S. aureus strain Mu50 taken from GenBank

SEQ ID No:16

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124861 agttttactg cctggaaatg ataaaagtaa atttcaacag cgtagttatg aggggttaga
124921 tgtgtttttt gttcaagaaa aaagagataa gcacgatata ttttatactg ttggtggtgt
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125041 aaagggtgaa gatgcttttg tgaaaggtta cccttattac attaaaaaag aaaaaataac
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125161 aacaatctca aaagatggta gggtcaaaat tagcttgaaa gatggcagtt tttataacct
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125281 taaagatatt gaagttaact taaagtaaat aattacgaat aataaaaagt aattgaagcg
125341 gcttaacggt gaaatgtaaa ttggtgcgca tagcttatac aaaaaggatg catcaatcga
125401 tatcgtcgtt aagccgtttt tgtttgtgtg tcatgaatcc tatcccaatc tccatgaata
125461 taaaaattcc accaccaaca tcaaaattct ccacatcgca acataaccaa atgttataat
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125581 actgaaaaac aacgtcagca acaagctgaa ttacataaaa aattatggtc gattgcgaat
125641 gatttaagag ggaatatgga tgcgagtgaa ttccgtaatt acatttttagg cttgattttc
125701 tatcgcttct tatctgaaaa agcggaacaa gaatatgcag atgccttgtc aggtgaagat
125761 attacgtatc aagaagcatg ggcagatgaa gaatatcgtg aagacttaaa agctgaatta
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125941 tcaacactag gtgaagaaag tgaaaatgac tttatcggac tgttcagcga tatggactta
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126181 tatacaccac aacaagtatc taagatactg gcgaagattg tcacagacgg taaagataaa
126241 ttacgtcacg tgtatgaccc aacatgtggt tcaggttcat tattgttacg tgttggtaaa
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126541 ggcaagcttg cgccaaaatc caaagcagac tttgccttta ttcaacatat ggtacattac
126601 ctagacgatg aaggtaccat ggcagttgta ctcccacatg gtgtcttatt ccgtggtgcc
126661 gcagaaggcg tcattcgtcg ttatttaatt gaagaaaaga actacttaga agccgtgatt
126721 ggcttaccag tgaatatttt ctatgggaca agtattccaa catgtatctt agtatttaaa
126781 aaatgttgcc aacaagacga caacgtatta tttatcgatg catccaatga ttttgaaaaa
126841 ggaaaaaatc aaaaccattt aagcgatgcc caagtcgaac gtattattga cacatacaag
126901 cgtaaagaaa caattgataa atacagttac agtgcgacat tacaagagat tgccgataac
126961 gattacaacc taaacatacc gaggtatgtc gatacattcg aagaagaagc gccaattgat
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127201 ggatcttaca gatagagtaa ttaggaaaaa taaaaactta gaatcgaaaa agcctttaac
127261 aatatccgga cagttaggtt taattgatca aacagaatat tttagtaaat cagtttcgtc
127321 gaaaaatcta gaaaattata cactaataaa gaatggagaa ttcgcgtata acaaaagtta
127381 ttctaatgga tacccattag ggctattaa aagattaact agatatgata gtggtgtatt
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127501 atattttgat tcgacacact ggtatagaga agtttctgga attgcagttg agggtgcaag
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127681 attagaagaa caaaagcttg aattacttca acaacagaaa aaaggctata tgcagaaaat
127741 tttctcacag gaactgcgat tcaaagatga gaatggtgaa gattatccag attgggaaaa
127801 tagcaaaata gaaaaatatt taaaagagag aaacgaacgt tctgacaaag ggcaaatgct
127861 ttcagtaact ataaatagtg gcattataaa atttagtgaa ttggatagaa aagataattc
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128161 cttaaaatat aaacaattaa aaaatataaa tatagatata cctgtattgg aggaacaaga
128221 aaagataggt gatttcttta aaaaaatgga tatattgata agtaaacaga aaatgaaaat
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128401 agtgaattaa aaacgaacat taaatttagg cactgtgaaa gcgcagtgtc ttttttgtgt
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128581 acttaataat gattaatttt tagttaaagt aagtttaatg tgaagcacga ccattgctca
128641 ttataatgaa tgaggattgt tcgtattgcg taatagaata aatcaaatag actaaaaatt
128701 gggagcatag aattatgaaa ttaaaaaata ttgctaaagc aagtttagca ctagggattt
128761 taacaacagg tatgattaca actactgctc agccagtaaa agcaagtaca ttagaggtta
128821 gatcacaagc tactcaagac ttgagtgaat attataaagg gagaggattt gaattaacaa
128881 atgtaacagg atataaatac ggaaataaag ttacatttat agataattct caacaaattg
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129061 gaattacaaa gacaaatggg actcaacata aagatactgt tcaaaacgtt aatttgtcag
129121 tttctaagag tacaggtcaa cacactactt ctgtgacttc agaatactat agcatctata
129181 aagaagaaat ctcattaaaa gaacttgatt ttaaattaag aaagcattta attgataaac
129241 atgatcttta taagacagaa cctaaagaca gtaaaattag aattactatg aaaaacggtg
129301 gctattatac atttgaatta aataaaaaat tacagcctca tcgcatgggt gatacgattg
129361 atagtagaaa tatagagaaa attgaagtga atttataata atattcgagg gagtatatca
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SEQ ID No:17 – SSL1

Gene	/gene="(set6) Mu50*ssl1*"
CDS	116916..117596
	/gene="(set6)Mu50*ssl1*"

/note="Pathogenicity island SaPIn2 SAV0422"
/codon_start=1
/transl_table=11
/product="(exotoxin 6) SSL1"
/protein_id="BAB56584.1"
/db_xref="GI:14246190"

/translation="MKFKAIAKASLALGMLATGVITSNVQSVQAKTEVKQQSESELKH
YYNKPVLERKNVTGYKYTEKGKDYIDVIVDNQYSQISLVGSDKDKFKDGDNSNIDVFI
LREGDSRQATNYSIGGVTKTNSQPFIDYIHTPILEIKKGKEEPQSSLYQIYKEDISLK
ELDYRLRERAIKQHGLYSNGLKQGQITITMKDGKSHTIDLSQKLEKERMGDSIDGRQI
QKILVEMK"

SEQ ID No:18 - SSL2

gene 117882..118577
/gene="(set7) Mu50*ssl2*"
CDS 117882..118577
/gene="(set7) Mu50*ssl2*"
/note="Pathogenicity island SaPIn2 SAV0423"
/codon_start=1
/transl_table=11
/product="(exotoxin 7) SSL2"
/protein_id="BAB56585.1"
/db_xref="GI:14246191"

/translation="MKMKNIAKISLLLGILATGVNTTTEKPVHAEKKPIVISENSKKL
KAYYTQPSIEYKNVTGYISFIQPSIKFMNIIDGNSVNNLALIGKDKQHYHTGVHRNLN
IFYVNEDKRFEGAKYSIGGITSANDKAVDLIAEARVIKADHIGEYDYDFFPFKIVKEA
MSLKEIDFKLRKYLIDNYGLYGEMSTGKITVKKKYYGKYTFELDKKLQEDRMSDVINV
TDIDRIEIKVRKA"

SEQ ID No:19 - SSL3

gene 118868..119938
/gene="(set8) Mu50*ssl3*"
CDS 118868..119938
/gene="(set8) Mu50*ssl3*"
/note="Pathogenicity island SaPIn2 SAV0424"
/codon_start=1
/transl_table=11
/product="(exotoxin 8)SSL3"
/protein_id="BAB56586.1"
/db_xref="GI:14246192"

/translation="MNMKTIAKTSLALGLLTTGAITVTTQSVKAEKIQSTKVDKVPTL
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QKSLNISATPAPKQEQSQTTTESTTPKTKVTTPPSTNTPQPMQSTKSDTPQSPTIKQA
QTDMTPKYEDLRAYYTKPSFEFEKQFGFLLKPWTTVRFMNVIPNRFIYKIALVGKDEK
KYKDGPYDNIDVFIVLEDNKYQLKKYSVGGITKTNSKKVDHKAELSVTKKDNQGMISR
DVSEYMITKEEISLKELDFKLRKQLIEKHNLYGNMGSGTIVIKMKNGGKYTFELHKKL
QEHRMADVIEGTNIDKIEVNIK"

SEQ ID No:20 - SSL5

gene 120302..121006
/gene="(set10) Mu50*ssl5*"
CDS 120302..121006
/gene="(set10) Mu50*ssl5*"
/note="Pathogenicity island SaPIn2] SAV0425"

/codon_start=1
/transl_table=11
/product="(exotoxin 10)SSL5"
/protein_id="BAB56587.1"
/db_xref="GI:14246193"

/translation="MKMAAIAKASLALGILATGTITSLHQTVNASEHEAKYENVTKDI
FDLRDYYSGASKELKNVTGYRYSKGGKHYLIFDKNRKFTRVQIFGKDIERFKARKNPG
LDIFVVKEAENRNGTVFSYGGVTKKNQDAYYDYINAPRFQIKRDEGDGIATYGRVHYI
YKEEISLKELDFKLRQYLIQNFDLYKKFPKDSKIKVIMKDGGYYTFELNKKLQTNRMS
DVIDGRNIEKIEANIR"

SEQ ID No:21 - SSL7

gene 121452..122147
/gene="(set11) Mu50*ssl7*"
CDS 121452..122147
/gene="(set11) Mu50*ssl7*"
/note="Pathogenicity island SaPIn2
SAV0426"
/codon_start=1
/transl_table=11
/product="(exotoxin 11)SSL7"
/protein_id="BAB56588.1"
/db_xref="GI:14246194"

/translation="MKLKTLAKATLALGLLTTGVITSEGQAVHAKEKQERVQHLYDIK
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VFVVKELIDPNGRLSTVGGVTKKNNKSSETNTHLFVNKVYGGNLDASIDSFLINKEEV
SLKELDFKIRKQLVEKYGLYKGTTKYGKITINLKDEKKEVIDLGDKLQFERMGDVLNS
KDIQNIAVTINQI"

SEQ ID No:22 - SSL8

gene 122486..123184
/gene="(set12) Mu50*ssl8*"
CDS 122486..123184
/gene="(set12) Mu50*ssl8*"
/note="Pathogenicity island SaPIn2
SAV0427"
/codon_start=1
/transl_table=11
/product="(exotoxin 12)SSL8"
/protein_id="BAB56589.1"
/db_xref="GI:14246195"

/translation="MKFTAIAKAIFVLGILTTSVMITENQSVNAKGKYEKMNRLYDTN
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VFAVPELVDLDGRIFSVSGVTKKNVKSIFESLRTPNLLVKKIDDKDGFSIDEFFFIQK
EEVSLKELDFKIRKLLIKKYKLYEGSADKGRIVINMKDENKYEIDLSDKLDFERMADV
INSEQIKNIEVNLK"

SEQ ID No:23 - SSL9

gene 123561..124259
/gene="(set13) Mu50*ssl9*"
CDS 123561..124259
/gene="(set13) Mu50*ssl9*"
/note="Pathogenicity island SaPIn2
SAV0428"
/codon_start=1
/transl_table=11
/product="(exotoxin 13)SSL9"
/protein_id="BAB56590.1"

/db_xref="GI:14246196"

/translation="MKLTALAKATLALGILTTGVFTAESKAVHAKVELDETQRKYYIN MLHQYYSEESFESTNISVKSEDYYGSNVLNFNQRNKTFKVFLLGDDKNKYKEKTHGLD VFAVPELIDIKGGIYSVGGITKKNVRSVFGFVSNPSLQVKKVDAKHGFSINELFFIQK EEVSLKELDFKIRKMLVEKYRLYKGASDKGRIVINMKDEKKYVIDLSEKLSFDRMFDV MDSKQIKNIEVNLN"

SEQ ID No:24 - SSL10

gene 124625..125308
/gene="(set14) Mu50*ssl10*"
CDS 124625..125308
/gene="(set14) Mu50*ssl10*"
/note="Pathogenicity island SaPIn2 SAV0429"
/codon_start=1
/transl_table=11
/product="(exotoxin 14)SSL10"
/protein_id="BAB56591.1"
/db_xref="GI:14246197"

/translation="MKFTALAKATLALGILTTGTLTTEVHSGHAKQNQKSVNKHDKEA LYRYYTGKTMEMKNISALKHGKNNLRFKFRGIKIQVLLPGNDKSKFQQRSYEGLDVFF VQEKRDKHDIFYTVGGVIQNNKTSGVVSAPILNISKEKGEDAFVKGYPYYIKKEKITL KELDYKLRKHLIEKYGLYKTISKDGRVKISLKDGSFYNLDLRSKLKFKYMGEVIESKQ IKDIEVNLK"

SEQ ID No:25 - SSL11

gene 128715..129398
/gene="(set15) Mu50*ssl11*"
CDS 128715..129398
/gene="(set15) Mu50*ssl11*"
/note="Pathogenicity island SaPIn2 SAV0433"
/codon_start=1
/transl_table=11
/product="(exotoxin 15)SSL11"
/protein_id="BAB56595.1"
/db_xref="GI:14246201"

/translation="MKLKNIAKASLALGILTTGMITTTAQPVKASTLEVRSQATQDLS EYYKGRGFELTNVTGYKYGNKVTFIDNSQQIDVTLTGNEKLTVKDDDEVSNVDVFVVR EGSDKSAITTSIGGITKTNGTQHKDTVQNVNLSVSKSTGQHTTSVTSEYYSIYKEEIS LKELDFKLRKHLIDKHDLYKTEPKDSKIRITMKNGGYYTFELNKKLQPHRMGDTIDSR NIEKIEVNL"

S. aureus strain MW2 taken from GenBank

SEQ ID No:26 - SSL1

139029..139709
/gene="(set16)MW2*ssl1*"
CDS 139029..139709
/gene="(set16) MW2*ssl1*"
/note="ORFID:MW0382 exotoxin homolog [Genomic island nu Sa alpha2]"
/codon_start=1
/transl_table=11
/protein_id="BAB94247.1"
/db_xref="GI:21203547"

/translation="MKFKAIAKASLALGMLATGVITSNVQSVQAKTEVKQQSEADLKL

YYNGPSFEYKKVTGYGFIEGKDRFIDFIYNGQYNKISLVGSDKDKYNEEVNPDIDVFV
VREGNGRQADNHSIGGITKTNRGVYYDYIHTPILEIKKGKEEPQSSLYQIYKEDISLK
ELDFKLRKQLISQSGLYSNGLKQGQITITMNDGTTHTIDLSQKLEKERMGESIDGRQI
QKILVEMK"

SEQ ID No:27 - SSL2

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     gene              139995..140690
                       /gene="(set17) MW2ssl2"
     CDS               139995..140690
                       /gene="(set17) MW2ssl2"
                       /note="ORFID:MW0383
                       exotoxin homolog [Genomic island nu Sa alpha2]"
                       /codon_start=1
                       /transl_table=11
                       /protein_id="BAB94248.1"
                       /db_xref="GI:21203548"
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/translation="MKMKSIVKISLLLGILATGVNTTTEKPVHAEKKPIVISENSKKL
KAYYTQPSIEYKNVTGYISFIQPSIKFMNIIDGNSVNNIALIGKDKQHYHTGVHRNLN
IFYVNEDKRFEGAKYSIGGITSANDKAVDLIAEARVIKADHIGEYDYDFFPFKIDKEA
MSLKEIDFKLRKYLIDNYGLYGEMSTGKITVKKKYYGKYTFELDKKLQEDRMSDVINV
TDIDRIEIKVRKA"

SEQ ID No:28 - SSL3

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     gene              140981..142051
                       /gene="(set18) MW2ssl3"
     CDS               140981..142051
                       /gene="(set18) MW2ssl3 "
                       /note="ORFID:MW0384
                       exotoxin homolog [Genomic island nu Sa alpha2]"
                       /codon_start=1
                       /transl_table=11
                       /protein_id="BAB94249.1"
                       /db_xref="GI:21203549"
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/translation="MKMRTIAKTSLALGLLTTGAITVTTQSVKAEKIQSTKVDKVPTL
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QKTLNISATPAPKQEQSQTTTESTTQQTKMTTPPSTNTPQPMQSTKSDTPQSPTIKQA
QTDMTPKYEDLRAYYTKPSFEFEKQFGFLLKPWTTVRFMNVIPNRFIYKIALVGKDEK
KYKDGPYDNIDVFIVLEDNKYQLKKYSVGGITKTNSKKVNHKVELSITKKDNQGMISR
DVSEYMITKEEISLKELDFKLRKQLIEKHNLYGNMGSGTIVIKMKNGGKYTFELHKKL
QEHRMADVIDGTNIDNIEVNIK"

SEQ ID No:29 - SSL4

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     gene              142416..143363
                       /gene="(set19) MW2ssl4 "
     CDS               142416..143363
                       /gene="(set19) MW2ssl4"
                       /note="ORFID:MW0385
                       exotoxin homolog [Genomic island nu Sa alpha2]"
                       /codon_start=1
                       /transl_table=11
                       /protein_id="BAB94250.1"
                       /db_xref="GI:21203550"
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/translation="MKITTIAKTSLALGLLTTGVITTTTQAANATTPPSTKVETPQQV
ANATTPSSTKVEAPQQAANATTPSSTKVEAPQSKPNATTPSSTKVEAPQQAANATTPP
SSNVDTSPPQSPTTKQVPTEINPKFKDLRAYYTKPSLEFKNEIGIILKKWTTIRFMNV
VPDYFIYKIALVGKDDKKYGEGVHRNVDVFVVLEENNYNLEKYSVGGITKSNSKKVDH
KAGVRITKEDNKGTISHDVSEFKITKEQISLKELDFKLRKQLIEKNNLYGNVGSGKIV
IKMKNGGKYTFELHKKLQENRMADVIDGTNIDNIEVNIK"

<u>SEQ ID No:30 - SSL5</u>

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    gene            143727..144431
                    /gene="set20 MW2ssl5"
    CDS             143727..144431
                    /gene="(set20) MW2ss5 "
                    /note="ORFID:MW0386
                    exotoxin homolog [Genomic island nu Sa alpha2]"
                    /codon_start=1
                    /transl_table=11
                    /protein_id="BAB94251.1"
                    /db_xref="GI:21203551"

/translation="MKMAAIAKASLALGILATGTITSLHQTVNASEHEAKYENVTKDI
FDLRDYYSGASKELKNVTGYRYSKGGKHYLIFDKHQKFTRIQIFGKDIERFKARKNPG
LDIFVVKEAENRNGTVFSYGGVTKKNQDAYYDYINAPRFQIKRDEGDGIATYGRVHYI
YKEEISLKELDFKLRQYLIQNFDLYKKFPKDSKIKVIMKDGGYYTFELNKKLQTNRMS
DVIDGRNIEKIEANIR"
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<u>SEQ ID No:31 - SSL6</u>

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    gene            144877..145575
                    /gene="(set21) MW2ssl6"
    CDS             144877..145575
                    /gene="(set21) MW2ssl6"
                    /note="ORFID:MW0387
                    exotoxin homolog [Genomic island nu Sa alpha2]"
                    /codon_start=1
                    /transl_table=11
                    /protein_id="BAB94252.1"
                    /db_xref="GI:21203552"

/translation="MKLKALAKATLVLGLLATGVITTESQTVKAAESTQGQHNYKSLK
YYYSKPSIELINVDGLYRQHLTDKGAYVWKNLKDYYIGLLGEDSKKFKSDVYGDLDAF
LVIEEEPVKGRQYSIGGISKTNSKEFKEREVDVKVTRKADRDTTSTKDSKFKITKEEI
SLKELDFKLRQKLMKEENLYDAINHRKGKIVVKMEDDKFYTFELTKKLQPHRMGDTID
GTKIKEINVELEYK"
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<u>SEQ ID No:32 - SSL7</u>

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    gene            145997..146692
                    /gene="(set22)MW2ssl7"
    CDS             145997..146692
                    /gene="(set22) MW2ssl7"
                    /note="ORFID:MW0388
                    exotoxin homolog [Genomic island nu Sa alpha2]"
                    /codon_start=1
                    /transl_table=11
                    /protein_id="BAB94253.1"
                    /db_xref="GI:21203553"

/translation="MKLKTLAKATLALGLLTTGVITSEGQAVQAKEKQERVQHLYDIK
DLHRYYSSESFEFSNISGKVENYNGSNVVRFNQENQNHQLFLSGKDKDKYKEGLEGQN
VFVVKELIDPNGRLSTVGGVTKKNNQSSETNTPLFIKKVYGGNLDASIESFLINKEEV
SLKELDFKIRQHLVKNYGLYKGTTKYGKITFNLKDGEKQEIDLGDKLQFEHMGDVLNS
KDIQNIAVTINQI"
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<u>SEQ ID No:33 - SSL8</u>

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    gene            147031..147729
                    /gene="(set23) MW2ssl8"
    CDS             147031..147729
                    /gene="(set23) MW2ssl1 "
                    /note="ORFID:MW0389
                    exotoxin homolog [Genomic island nu Sa alpha2]"
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/codon_start=1
/transl_table=11
/protein_id="BAB94254.1"
/db_xref="GI:21203554"

/translation="MKFTAIAKAIFVLGILTTSVMITENQSVNAKGKYEKMNRLYDTN KLHQYYSGPSYELTNVSGQSQGYYDSNVLLFNQQNQKFQVFLLGKDENKYKEKTHGLD VFAVPELVDLDGRIFSVSGVTKKNVKSIFESLRTPNLLVKKIDDKDGFSYDEFFFIQK EEVSLKELDFKIRKLLIKKYKLYEGAADKGRIVINMKDENKYEIDLSDKLGFERMADV INSEQIKNIEVNLK"

SEQ ID No:34 - SSL9

gene 148108..148806
/gene="(set24) MW2*ssl9*"
CDS 148108..148806
/gene="(set24) MW2*ssl9*"
/note="ORFID:MW0390
exotoxin homolog [Genomic island nu Sa alpha2]"
/codon_start=1
/transl_table=11
/protein_id="BAB94255.1"
/db_xref="GI:21203555"

/translation="MKFTALAKATLALGILTTGVFTTESKAVHAKVELDETQRKYYIN MLHQYYSEESFEPTNISVKSEDYYGSNVLNFKQRNKAFKVFLLGDDKNKYKEKTHGLD VFAVPELIDIKGGIYSVGGITKKNVRSVFGFVSNPSLQVKKIDPKHGFSINELFFIQK EEVSLKELDFKIRKMLVEKYRLYKGASDKGRIVINMKDEKKYVIDLSEKLSFDRMFDV MDSKQIKNIEVNLN"

SEQ ID No:35 - SSL10

gene 149165..149848
/gene="(set25) MW2*ssl10*"
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S. aureus strain NCTC8325 taken from uncompleted genome project at Oklahoma University via http://pedant.gsf.de

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59465 TTCTTT TTGACTGTAA TTTTTCCTGT ACTCATTTCA CCGTAAAGAC CATAATTATC AATAAGGTAT TTTC
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59675 CTCGTG ATACCCCCAA TAGAGTACTT TGCACCTTCA AATCTCTTAT CCTCATTAAC GTAAAATATA TTAA
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59885 TCAATA CTAGGTTGAT TATAATAAGC TTTTAATTTT TTGCTATTTT CACTTATTAC AATAGGTTTC TTTT
59955 CGGCAT GAACTGGTTT TTCCGTTGTA GTGTTTACAC CTGTTGCTAA TATTCCTAAT AACAAACTTA TTTT
60025 TGCAAT ATTTTTCATT TTCATAGTTG TATGCTCCAA TCTATTATAA TTAGATTGTT TTATTACGTA ATTT
60095 GAATCA TACACCCATA TTATAGGAGC TGTATTCGGA TATTCACATT AACCTGTTTT TAACTATTCA TAAA
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60375 TTGACT CACCCATACG TTCTTTTTCA AGTTTTTGAC TTAAATCGAT TGTATGTGTT GTGCCATCAT TCAT
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61355 ATAATA TTTACGTATT TACTATACAC GTCGACAATA AATACAGATT AGAATTTTTT ATAAAATCAA ATGT
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61635 AGATTA TTTTAATCAA
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SEQ ID No:38 - SSL1

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/gene=" NCTC8325*ssl1*"
CDS complement 60331..61026
/gene="NCTC8325*ssl1*
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SEQ ID No:39 - SSL2

gene 59350..60045
/gene=" NCTC8325*ssl2*"
CDS complement 59350..60045
/gene="NCTC8325*ssl2*
/product="(SET7)SSL2"
/translation="MKMKNIAKISLLLGILATGVNTTTEKPVHAEKKPIVISENSKKLKAYYNQPSIEYKNVTGYISFIQPSIKFMNIIDGNSVNNIALIGKDKQHYHTGVHRNLNIFYVNEDKRFEGAKYSIGGITSANDKAVDLIAEARVIKEDHTGEYDYDFFPFKIDKEAMSLKEIDFKLRKYLIDNYGLYGEMSTGKITVKKKYYGKYTFELDKKLQEDRMSDVINVTDIDRIEIKVIKA"

SEQ ID No:40 - SSL3

gene 57989..59059
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CDS complement 57989 …59059
/gene="NCTC8325*ssl3*
/product="(similar to SET8)SSL3"
/translation="MKMRTIAKTSLALGLLTTGAITVTTQSVKAEKIQSTKVDKVPTLKAERLAMINITAGANSATTQAANTRQERTPKLEKAPNTNEEKTSASKIEKISQPKQEEQKTLNISATPAPKQEQSQTTTESTTPKTKVTTPPSTNTPQPMQSTKSDTPQSPTIKQAQTDMTPKYEDLRAYYTKPSFEFEKQFGFMLKPWTTVRFMNVIPNRFIYKIALVGKDEKKYKDGPYDNIDVFIVLEDNKYQLKKYSVGGITKTNSKKVNHKVELSITKKDNQGMISRDVSEYMITKEEISLKELDFKLRKQLIEKHNLYGNMGSGTIVIKMKNGGKYTFELHKKLQEHRMADVIDGTNIDNIEVNIK"

SEQ ID No:41 - SSL4

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CDS complement 56698..57624
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DNIEVNIK"

<u>SEQ ID No:42 - SSL5</u>

<u>gene</u> 55630..56334
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<u>CDS</u> complement 55630..56334
/gene="NCTC8325*ssl5*
/product="(SET10)SSL5"
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<u>SEQ ID No:43 - SSL6</u>

<u>gene</u> 54489..55184
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<u>CDS</u> complement 54489...55184
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/product="(SET8)SSL6"
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KIDESSEKSKDSKFKITKEEISLKELDFKLRKKLMEEEKLYGAVNNRKGKIVVKMEDDKFYTFELTKKLQPHRMGD
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<u>SEQ ID No:44 - SSL7</u>

<u>gene</u> 53373...54068
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<u>CDS</u> complement 53373...54068
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VLNSKDINKIEVTLKQI"

<u>SEQ ID No:45 - SSL8</u>

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<u>CDS</u> complement 52331...53029
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<u>SEQ ID No:46 - SSL9</u>

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<u>CDS</u> complement 51253....51951
/gene="NCTC8325*ssl9*
/product="(SET13)SSL9"

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SEQ ID No:47 - SSL10

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/gene=" NCTC8325*ssl10*"
CDS complement 50204…50887
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SEQ ID No:48 - SSL11

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/gene=" NCTC8325*ssl11*"
CDS complement 46120..46797
/gene="NCTC8325*ssl11*
/product="(SET15)SSL11"

/translation="MKLKNIAKASLALGILTTGMITTTAQPVKASTLEVRSQATQDLSEYYNRPFFEYTNQSGYKE
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GRNIEKIEVNL"

SEQ ID No: 49

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1047513 GCCCAATG GTAGCATTCA TGCAACATTG CAAACGTGGG TTTGGTATAG TCATATTCAA GTGTTTGGAT CC
1047583 GAGAGTTG GGGAAACATT AATCAGTTAA GAAATAAATA CGTTGATATA TTTGGAACTA AAGATGAGGA CA
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1049403 CAAAGATA AACTACAAAC GATTATTGGT GCGCATAAAA TATACCAAGG CAATAAACCA GTATTAACAT TG
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SEQ ID No:50 - SSL12

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SEQ ID No:51 - SSL13

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     CDS              1048124.. 1048849
                      /gene="NCTC8325ssl13
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SEQ ID No:52 - SSL14

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     CDS              1048957.. 1049673
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S. aureus strain EMRSA 16(252) taken from unpublished genome project at the Sanger centre via http://pedant.gsf.de

SEQ ID No:53

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123159 AA CATAGTGATT TGGTAAAGTA GTTCCCGTTA TCTTTTGAGC TCCAGGTTTA ATAGTATCTA ATTTAACA
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125189 CG GTCGAGTTTG CTGAAGAAGT CACCTATTTT TCTCTGTTCT TTAGCCGAAA CAGGGTATAT GACCTTCA
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125889 TC GACATATCTC GGTATGTTTA AGTTGTAATC GTTATCGGCG ATCTCTTGTA ATGTCGCGCT GTAGCTAT
125959 AC TTATCAATTG TTTCCTTACG CTTATATGTG TCTATAATTC GTTCGACTTG GGCATCGCTT AAATGGTT
126029 TT GGTTTTTTCC TTTTTCAAAA TCATTGGATG CATCGATAAA TAATACGTTG TCGTCTTGTT GGCGACAT
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126239 AC CATGTGGGAG TACAACGGCC ATGGTACCTT CATCATCTAG GTAATGTACC ATGTGTTGAA TAAAGGCA
126309 AA GTCTGCTTTA GACTTTGGCG CAAGCTTGCC GTATCCGCTG AAGCGTTCGT CATTTTCAAA TTTTGAGT
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126799 AT GGTAAGTCAT CAAGGTTAAC CATAACTTTG GAAATTAACG CAGTACGTTC TTTGACATTG TTACCTAA
126869 AC GCGTTGAACT TAAGTCCATA TCGCTGAACA GTCCGATAAA GTCATTTTCA CTTTCTTCAC CTAGTGTT
126939 GA AGTTTCAACT TTACGAATTG CCGTCGCCAG ATGTTCGATA TCGAAATCTT GCGTTTCAAT TTCACGAA
127009 TC ATCGCACTGA ATAAATCTTG TGGCTCAATG AAGTAACCAA CTTGATCAAT TAATTCTGCT TTTAAGTC
127079 TT CACGGTATTC TTCATCTGCC CATGCTTCTT GATATGTAAT ATCTTCACCT GCCAAGGCAT CTGCATAT
127149 TC TTGTTCCGCT TTTTCAGATA AGAAGCGATA GAAAATCAAG CCTAAAATGT AATTACGGAA TTCACTCG
127219 CA TCCATATTCC CTCTTAAATC ATTCGCAATT GACCATAATT TTTTATGTAA TTCAGCTTGT TGCTGACG
127289 TT GTTTTTCAGT AATAGACATG TGATTCCTCC GCCTTTGCAT AAGTAATTTG TCTCTTTGTG TAATAGAT
127359 TT ATTATAACAT TTGGTGGTGT CGCGATGTTG AGAATTTTGA TGTTGATGGT GGAAATTTTA TATTCATG
127429 GA GATTGGGATA GGATTCATAA CACGCAAACA AAAACGGCTT AACGACGATA TCGATTGATG CATCCTTT
127499 TG GTAAGGTATA CGCACCAATT TACTTTTCAT CGTTAAGCCG CTTCAATTAC TTTTTATTAT TCATAATG
127569 AT TTACTTTAAA TTCACTTCAA TATCCTTAAT TTGTTTACTA TCTATGACTT CCCCCATATG TTTGAATT
127639 TT AATTTAGTTC TTAAATCAAG GTTATAAAAG CTACCATCTT TCAGACTAAT TTTAATCCTA CCATCTTT
127709 TG AGAGTGTTTT ATAAAGACCG TATTTTTCAA TTAGATGCTT TCTCAACTTA AAATCTAACT CTTTCAAT
127779 GA TATTTCTTCT TTTTTAATAT CATAAGGGTA ACCTTTCACA AAAGCATCTT CACCCTTTTC TTTTGTAA
127849 CA TTTAATCTTG GTGTGCTGAC AAAGCCGGAT GTTTTATTGG TCTTTGTTAC ACCACCAACA GTATATGA
127919 TA TGTCGTGCTT GTCTCTTCTT TCTTGAACAA AAAACACATC TAAGCCCGTA TGTCTTCGCT GTTGATAT
127989 TT ACGGTACTCA TCTCCAGGCA ATAATACTTG AGTCTTCATC CCTCTATATT TAAAACGTAA GTTATTTT
128059 TA CCATGTCTCA AAGCATTAAT GTTTTTCATT TCCTTAAAGT TTCCAGTGTA GTATCGGTGT AATGCTTC
128129 TT TGTCATGTTT GTTTACTGAC TTTTGATTTT GTTTAGCATG ACCTGAATGG GCCTCTGTTG TTAAAGTT
128199 CC TGTTGTTAAA ATCCCTAATG CTAATGTTAC TTTTGCTAAT GCTGTCAATT TCATATTTAT TTACTCCA
128269 AT CTTAATGTAT TGGATTGTTA TTATTACGTA ATTTGAATCA TATACGCTTA TTATAACGTC CATCGTTT
128339 AA CGCGATAATT AACCTCGATT TAAATATGCG TGAATTATTA TTAATTAAAA ACAAATATAT TTTAATGT
128409 CC AGGTTAATTA ACTTTCACGC TTTACATGTC GTTGTTTTTC CGGATCATCG TTTTCTACAA CTAATTGT
128479 GT TATTTCTACT CTTTGAAACG CAAAAAAACAA CTTAACAACA ATAATGTATT TAACACAGTT CTTATTCA
128549 AA GGTACGGGTG TCAATGCACA TTTTATCGTT AAGCCGCTTT TTAATTTTTT ATACTATCAT CTTTAATT
128619 AA TTCAAATTCA CTTCAATATT TTTAATCTGC TTACTATCCA GCACATCAAA CATACGATCA AAACTTAA
128689 TT TTTCACTTAA ATCAATTTCA TGTTTCTTTT CGTCTTTCAT ATTGATAACA ATTCTACCTT TATCTGAC
128759 GC GCCTTTATAC AATCTATATT TTTCGACTAA CATTTTTCTG ATTTTAAAAT CAAGTTCTTT CAATGATA
128829 CT TCTTCTTTTT GAATAAAGAA CAACTCTTTT ATCGAAAAGC CATCTTTAGG ATCAACTTTT TTAACTTG
128899 CA GTCCCGGATG ACTTACATAG CCAAACACGG ATCTCACATT TTTCTTTGTT ATACCGCCAA CGCTATAT
128969 AT GCCGCCTTTA GTATCTATTA ATTCAGGTAC TGCAAAGACA TCACGGCCAT GCGTCAGTTC TTTATATT
129039 TA TTTCTATCGT CGCCAATTAG AAATACTTTG AAATTTTTAT TTCGTTGGTT AAAGTTTAAA ACGTTAGA

129109 CC CATAATAATC TTCACTTTTA ACACTAATGT TTGTTGATTC ATAGCTTTCT TGAGAATAGT AATCTTTT
129179 AG CATATTTATA TAATATTTGC GTTGTGTTTC ATCCAACTTT ACTTTCGCGT TTACAGTTTG ACTTTCTG
129249 CT GTCATCACAC CTGTTGTTAA TATTCCTAAT GCTAATGTTG CTTTAGCTAT TGCTGTTAAT TTCATAAT
129319 TT ATTGCTCCAA TCTTAATGTA TTGGATTGTT ATGATTACGT AATTTGAAAC ATCTGCCTTT ATTATAAA
129389 GT GCATCGAAAC AAACTGACAT TAACGTGCGT TTAAATAACT TTGAATCATT GTTAATGAAC ACCTAATT
129459 AA TATTCAAAGT ACGTGGTTTT AATGAGTGGT ATGACTTATT TAGTATACTC GTGACTTGTG TTATCAAA
129529 TG TAAAAAACAG CCTAACGACG ACGTTGCTTT AAATACGCTC CTTTGATAGG ATATACATAT TTATTCAA
129599 CG TTTCATCGTT AAGCTGCCTC AAAATTTATT ACTTTAAAGT CATTGATTGC TTACTTTAAA TTTGGTTA
129669 AT AGTGACTGAT ATACCTCTAA TGTCTTTACT ATTCAACACA TCGCCCATGC GCTCGAATTG TAATTTAT
129739 CA CCTAAATCAA TTTCTACTTT ATTTTCGTCT TTCAAATTGA TAATGATTTT ACCGTATTTA GATGTACC
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129949 GT GTATTAGTTT CAGAAGTTTT GTTGTTTTTC TTCGTTACAC CACCAACAGT AGATAGTCTG CCGTTTGG
130019 AT CAATTAATTC TTGTACTACA AAGACATTTT GGCCTTGTAG ACCTTCTTTA TATTGTTCTT TATCTTTT
130089 CC TAATAAGAAT AATTGGTGAT TTTGATCTTT TGGGTTAAAG CGTACAACGT TAGAACCATT GTAGTTTT
130159 CA ACCTTACCAC TAACATTACT ATATTCGAAA CTTTCTGATG AGTAGTATCG ATGTAAATCT CTAATATC
130229 AT GTAAATGTTG TACTCTCTCT TGTTTTTCTG CCGCTTGAAC TGCTTGACCT TCTGATGTAA TGACACCA
130299 GT AGTTAATAAA CCTAATGCTA ATGTTGCTTT AGCTAACGTT TTTAATTTCA TAGTATTATT CTCCCAAT
130369 CT ATTTTTAAAT TTTGACTTAA TATATGTTTA TGTGATTAAT TCAATTACGT AATACGAACA ATCTACTA
130439 TC ATTATATAAG CCGGATACTG CGCTATGAAT TAACCGCTTT TTAACTATTC CTGAACCAAT GTTAAGCT
130509 AA TTAATGGAAT CCTAACAGTA TTAATCATTT TTTATAACTC TATGCTATTT TTTTCACCAT TCACACTT
130579 TC TTTCAATTTA ATTATGTTTT CCACATTGTT TCATGTCACT AGTGCGACAC CGTGCGACTA TAGGTATC
130649 AA CTATTTTCAC AGTTTTTATT GTCGTTATTA TCTTTCATCG ACCCACTTCA TTTCCGATCG TAACGACA
130719 CA AAAAAGAAGC TAAGCAACCT ATGCTGCCTA GCTCATCTAT ACTATCCATA TTTTACTATT ATCCATGT
130789 TT CGTTGAATTA TCTAATATTG GCTTCTATTT TCTCAATATT TCTGCCATCT ATGACGTCAC TCATTCGG
130859 TT TGTTTGTAAC TTTTTATTGA GTTCAAACGT ATAATAGCCG CCATCTTTCA TTGTCACTTT TATCTTGC
130929 TA GCTTTAGGAA ACTTTTTATA CAGATCAAAA TCTTGAATTA AATACTGTCG TAATTTAAAA TCAAGTTC
130999 TT TCAGCGAAAT CTCTTCCTTA TAAATGTAGT ATCTTTTAAC ATGCACAGAA ACACCTGCAC CTACTTCT
131069 TT TTTAATAACG AATCTAGGTG CGCTTAAGTA ATCATAGTAA GCGCCTTGAT TTTTCTTAGT AACGCCAC
131139 CA TATGAATACA CTGTGCCGTT GCGATTTTCC GCTTCTTTAA CTACAAATAT ATCTAATCCT GGATTTTT
131209 AC GTTTTTTAAT CCTTTCTATA TCTTTACCAA AAATTTGTAT TCTTGTGAAC TTTCTATTTT TATCAAAG
131279 AT AAGGTAGTGC TTGCCACCTT TGCTATAACG ATAGCCAGTA ACATTTTTAA GTTCCTTACT TGCGCGAC
131349 TA TAGTAATCTC TCAAGTCGAA GATATCTTTT GTCACATTTT CATATTTTGA TTCATGTTCG CTCGCATT
131419 TA CAGTTTGAGC CGTTGATGTT ATAACCCCAG TCGCTAAAAT ACTTAGAGCT AAACTGGCTT TCGCAATT
131489 GC TGTCATCTTC ATAGTTGTAT GCTCCAATCG TAATTATTAG ATTTGTTCGA TTACGTTTAT TGAATCAT
131559 AC AGCTTTATTA TAGTTGGCGT ATGTCTCTAT TCATATTAAA CCTTGTTTAA CTATATTTGA ATCATCGT
131629 TA ATTAAATTAA GGAATCCATA ATGTTCGTTA AATAAAAATG ACTTTTGTTG TACTTCAACG CTTGATAG
131699 AT TGGTATTTTT AGACACATTT AGGACATAAG CATGTTATGT GTGGTCAACA TCAAATATTC GTCTTCTT
131769 AT ACCACTGTGC AACACGAAAG AAGCTGAGCA ACATGTAAAT TTTTGTCACT CAACTTCTCG GTACATCG
131839 TT CAACGGTTCT ATGCAGTATC CATCACGATG ATTTTAGATT CACTTCAATT CTTTCGATAC TAGTGCCA
131909 TC TATGACATCT GCCATGCGAT GTTCTTGTAA TTTTTTATGC AATTCAAACG TGTACTTCCC ACCGTTTT
131979 TC GTTTTAATAA CAATTGTTCC TGAACCAATA TTACCGTACA AATTATGTTG TTCAATGAGT TGCTTTCT
132049 CA ATTTAAAATC AAGCTCTTTC AAGGAAATCT CTTCTTTAGT TATCTTATAT TCTGAATCAT CGTGTGAG
132119 AT TTTGCCTTTC TCATCTTTTT TAGTAATGCT TAATTCTGCT TTGTGATCAA CTTTTTTACT ATTTGTCT
132189 TC GTGATACCCC CGACAGAATA TTTTTTCAAT TGATATTTAT TGTCCTCTAA AACGATAAAT ACATCAAT
132259 AT TATCGTATGG CCCATCTTTA TATTTCTTAT CATCTTTTCC AACTAAAGCT ATTTTATAAA TGAACCAA
132329 TC TGGTATAACA TTCATAAACC TAACTGTCGT CCATGGTTTC AGCATAAAGC CAAATTGCTT TTCGAATT
132399 CT AAACTCGGTT TCGTATAATA TGTTCTTAAA TCCTTATATT TAGGGTTTAT TTCCTTTTGT GCTTGTTT
132469 TG TGGTTGGCGA TTGCGGTTGT TTTGTTTCGA CATTAGATGA ATGCGGTGTT GTTGGGTTTG GTGTTGGT
132539 TG TGGCGATTGC GGTTGTACAT TTGGTGAAGG CGGAGTTGTT ACACTTGGTG TTGGTTGTGG CGATTGCG
132609 GT TGTACATTTG GTGAAGGCGA TGTTGTTACT TTTTGTATTT TAGATTTTAT TGCCTGTTCT GTTTTAAG
132679 TG CTGATGCTAC TTCTGCATTA GCCGATTGCG TTGTTACTAT ACTTGCACCT GTTGTTAAAA GTGATAGT
132749 GC TAAACTGGTT TTCGCAATTT GTGTCATTTT CATAGTTGTA TGCTCCAATC TATTATATTC GATTGTTC
132819 TT TACGTAATTA GAATCATACA ACTACATTAT AGAAGACGTA TCGGTCTATT CACATTAAAC CATGTTTA
132889 AC TATATTTGAA TCATCGTTAA GTAATCCATA ATTTTCGTTA AATACAGATG GTTTCGAAGC GATTCAAC
132959 GC TTGCACATTG GGCATTGCAT CATTTTCAAG ACATTGAGAT GTCACTTTTA CAAACAAGTG AATAATTT
133029 CC CTTAACATCA TTACGCAAAA CAAAAGAAGC TAAGCAATGA TGTAGGTCAT TGTCGCTTAA CTTCTCAT
133099 TT CATCGTTCAA CGGTTCTATG TAGTATCCAT CACGATGATT TTAGATTCAC TTCAATTCTA TCAATATT
133169 TG TACCATCAAT AACATCTGCC ATGCGATGTT GTTGCAATTT TTTGTGTAAT TCAAACGTGT ACTTTCCA
133239 CC ATTTTTCATT TTAATAACGA TTGTTCCTGA ACCAATATTA CCGTACAAAT TATGTTGTTC AATGAGTT
133309 GT TTTCTCAATT TAAAATCAAG TTCTTTCAAG GAAATCTCTT CTTTAGTAAT CTTGTATTCT GAAACATC
133379 AT GTGAGATTGT ACCTTTTTTA TCTTCTTTAG TAATACTTAT TCCAGTTTTG TAATCAACTT TCTTTCTA
133449 TT TGCTTTTGTG ATACCACCGA CCGAGTATTT GTCTACGCCA TATTTATTTT GTTCTAAAAC GATAAATA
133519 CA TCGACATGCC TATGCACGCC TTCACCATAT TTCTTATCAT CTTTTCCAAC TAAAGCTATT TTATATAT
133589 GA AATAATCTGG AACAATATTC ATAAATCTTA TTGTTGTCCA TTTTTTGATA ATTATACCCA ACTCATTT
133659 TT AAATTCTAAA CTTGATTTCG TATAATATGA TCTTAAACCT TTAAATTTAG GGTTTATTTC CTTTTGTG
133729 CT TGTTTTGTGG TTGGCGATGT TGGTTGTGGT GTTTCGACAT TAGATGAAGG CGGTGTTGTT ACACTTGG
133799 TG TTGGTTGTGT TGATTGCGGT TGTGCATTTG GTAAAGACTG AGTTGTTCCG CTTGGTGCTG GTTGTGTT
133869 GC TTTTTGTATG TTAGATTTTG GCGTCTGTTC TGTTTGAGTT GAAAGCGATG TTGATACATT TTCTGTGT
133939 TA GACTTTGCCG CCTGTTCAGG ATTAGCCGTA TGATTTTGTT CTGCGTTCAC TGCTTGCGCT GTCGTTGT
134009 GA TTGCGCTTGT TGATACGTTT ATCTTTGCTA ACTGTCCTGC TTTAAGTGCT GATGCTACTT CTGCATTG
134079 GC CGATTGCGTT GTTACTATAC TTGCACCTGT TGTTACAAGC CCTAACGCTA TACTCGCTTT CGCAATTG
134149 TT CTTATTTTCA TAGTTGTATG CTCCAATCGT AATTATTCGA TTGTTCTTTA CGTAATTAGA ATCATACA

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134219 AC TTCATTATAG AGGACATATT GGTCTATTCA CATTAACCCT CGTTTAACAA TTGTTGAAAT ATTATTAA
134289 GT CATTTAAGCA AAAAATAATG AGTACTTTCG AGGTTTATGT GGTGTTACTA TGTATCTTTG AAATGATT
134359 TT AAGACATAAA AAAGAAGTTA AGTAACGTTT TATCATCACT TAACCTCACT ATTGCAATTT CAATTCAT
134429 TA CGACGACCAG TCTAAGCATT ATGCTTTTTT AACTTTGACT TCAATCCTAT CAATATCTAT GACTTTGA
134499 CG ATATCGGCCA TTCGGTCTTC TTGTAACTTT TTATCCAATT CAATTGTATA CTTGCCATAG TATTTCAT
134569 TT GGACAGTAAC TGTTCCTGAA CTCATTTCAC CATAAAGACC ATAATGATCA ATAAGATGTT TTCTTATT
134639 TT AAAATCAACC TCTTTTAATG TCATTGCTTC TTTATCTATT TTAAATGGGA AAAAGTCATA ATCATATT
134709 CA CCAGTGTGAT CTTCTTTAAT GACTCTTGCT TCTGCTACTT GGTCGACAAC TTTATCGCTT GCTTTTGT
134779 GA TACCACCAAT CGAGTACTTT GCACCTTCAA ATCTCTTATC CTCATTAACA TAAAATATAT CAAGGTTG
134849 CG ATGTACACCC GTATGATAGT GTTCCTTATC TTTGCCAACT AAAGCTAGAT TATTAACTGT ATTACCTT
134919 CT ATCATATTCA AAAATTTAGT GCCTGGTTTA GGTTGAATAC TACTGATATA ACCTGTCACA TTTTTATA
134989 TT CAACACTAGG TTGAGTATAG TACGCTTTTA AATTTTTACT ATTTTGGCTT ACTTGAACAT GTTTATTT
135059 TC GGCATGCACC GGTTGTTCCG TTACAGTATT TACACCTGTA GCTAAAATAC CCAACACTAA ACTTACTT
135129 TT GCAATTGATT TCATTTTCAT AATTGTATGC TCCAATATAT TAGATTAGAT TGTTTTATTA CGTAAATT
135199 GA ATCATACAAC CATATTATAG GAGCTGTATG CTGATATTCA CATTAACCCT TTTTTAACTA TTCATAAA
135269 AT ATGATTAAGC TAGTTAAGTA AAAGATAATG CGTGCTGCGA CTGTTTGTGT GAGTTTTGTA ACTTTGCC
135339 CT CAAAAAAGAA GCTAAGCAAC AGTACGTCGC TTAACTTCCA TATATTTCCA TAACAAGCAC GATTCAAC
135409 AT AGCGCTTTGT CGTTAGAAAG TATTATTTCA TTTCTACTAG AATTTTTTGT ATTTGTCTGC CGTCGATA
135479 GA ATCACCCATA CGTTCTTTTT CAAGTTTTTG ACTTAAATCG ATAGTATGTG ATTTGCCATC TTTCATAG
135549 TA ATTGTAATTT GACCTTGTTT AAGACCATTT GAATACAATC CGTGTTGTTT GATTGCACGT TCTCGTAA
135619 TC TATAATCAAG TTCTTTTAAT GAGATATTTT CTTTATAAAT TTGATACAGA CTATTTGTGG GTTCTTCA
135689 TT ACCTTTCTTA ATTTCAAGGA TTGGAGAGTG TATATAGTCG TAATACACTC CTCTATTAGT TTTTGTTA
135759 CG CCACCAATCG AATGATTATC AGCTTGTCTA CCGTTTCCTT CTCTAACGAC AAACACATCT ATATCTGG
135829 GT TAACTTCTTC ATTATATTTA TCTTTATCAG AACCAACTAA AGATATTTTA TTATATTGTC CATTGTAT
135899 AT AAAATCAATG AATCTATCTT TACCTTCAAT AAATCCATAT CCAGTTACTT TTTTATATTC AAAACTTG
135969 GT CCATTATAAT AAAGTTTTAA ATCAGCCTCA CTTTGTTGTT TAACTTCTGT TTTCGCTTGT ACTGATTG
136039 TA TATTCGACGT TATTACACCT GTTGCTAACA TTCCCAATGC TAAACTTGCT TTTGCTATCG CTTTAAAT
136109 TT CATAATTTTT AGCCCCAATC TATTTAAATT TGATTTTTCA ATTACGTAAT ATGAACAATC TACCTACA
136179 TT ATATTGAGGC GCTATTCCCT TTCAAATTAA ACCTCATTTA ACTAAACTTG AATCATTGTT AAGGTAAT
136249 TA ATAAAATGCT AACTGTTAAT AATCAATTCT TATCCGTCAA GACTCTTTTT TATACAATTC ACACTTTA
136319 AA CCATTTTAAT TTTAAAAACT GTAAAACTTT CAGACACAAA AATGACATCA TATCGTCGCA GTACCATG
136389 TC AAAATTTTCA AAGATCATGG TGACACGCAT CAACTAAAAC GCGTCATTAC GGTATTTTTA ACATTAAT
136459 AA CATATGCGTA TTTACTATAC ACGGCGACAA TAAATACAGA TTGCAATTTT TTATAAAATC AAATGTTT
136529 TG AAAATCATCG AATAAGTATT ATGTTATGTA TATAAAGATT AGGAGATGAA GTGAATGAAT ATTATGTT
136599 AA CAGGTGCTAC AGGTCATTTA GGCACACATA TTACAAATCA AGCCATTGCA
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SEQ ID No:54 - SSL1

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CDS complement 135433..136128
/gene="EMRSA 16(252)*ssl1*
/product="(similar to SET6 from strain Mu50)SSL1"

/translation="MGLKIMKFKAIAKASLALGMLATGVITSNIQSVQAKTEVKQQSEADLKLYYNGPSFEYKKVT
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PILEIKKGNEEPQNSLYQIYKENISLKELDYRLRERAIKQHGLYSNGLKQGQITITMKDGKSHTIDLSQKLEKERM
GDSIDGRQIQKILVEMK"

SEQ ID No:55 - SSL2

gene 134449..135150
/gene="EMRSA 16(252)*ssl2*"
CDS complement 134449..135150
/gene="EMRSA 16(252)*ssl2*
/product="(similar to SET7 from strain N315)SSL2"

/translation="MKMKSIAKVSLVLGILATGVNTVTEQPVHAENKHVQVSQNSKNLKAYYTQPSVEYKNVTGYI
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RVIKEDHTGEYDYDFFPFKIDKEAMTLKEVDFKIRKHLIDHYGLYGEMSSGTVTVQMKYYGKYTIELDKKLQEDRM
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SEQ ID No:56 - SSL3

gene 133130..134161
/gene="EMRSA 16(252)*ssl3*"

<u>CDS</u> complement 133130..134161
/gene="EMRSA 16(252)*ssl3*
/product="(similar to SET9 from strain N315)SSL3"

/translation="MKIRTIAKASIALGLVTTGASIVTTQSANAEVASALKAGQLAKINVSTSAITTTAQAVNAEQ
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SPTTKQAQKEINPKFKGLRSYYTKSSLEFKNELGIIIKKWTTIRFMNIVPDYFIYKIALVGKDDKKYGEGVHRHVD
VFIVLEQNKYGVDKYSVGGITKANRKKVDYKTGISITKEDKKGTISHDVSEYKITKEEISLKELDFKLRKQLIEQH
NLYGNIGSGTIVIKMKNGGKYTFELHKKLQQHRMADVIDGTNIDRIEVNLKSS"

<u>SEQ ID No:57 - SSL4</u>

<u>gene</u> 131863..132783
/gene="EMRSA 16(252)*ssl4*"
<u>CDS</u> complement 131863..132783
/gene="EMRSA 16(252)*ssl4*
/product="(similar to SET8 from strain Mu50)SSL4"

/translation="MKMTQIAKTSLALSLLTTGASIVTTQSANAEVASALKTEQAIKSKIQKVTTSPSPNVQPQSP
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KPWTTVRFMNVIPDWFIYKIALVGKDDKKYKDGPYDNIDVFIVLEDNKYQLKKYSVGGITKTNSKKVDHKAELSIT
KKDEKGKISHDDSEYKITKEEISLKELDFKLRKQLIEQHNLYGNIGSGTIVIKTKNGGKYTFELHKKLQEHRMADV
IDGTSIERIE
VNLKSS"

<u>SEQ ID No:58 - SSL5</u>

<u>gene</u> 130798..131502
/gene="EMRSA 16(252)*ssl5*"
<u>CDS</u> complement 130798..131502
/gene="EMRSA 16(252)*ssl5*
/product="(similar to SET3)SSL5"

/translation="MKMTAIAKASLALSILATGVITSTAQTVNASEHESKYENVTKDIFDLRDYYSRASKELKNVT
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PRFVIKKEVGAGVSVHVKRYYIYKEEISLKELDFKLRQYLIQDFDLYKKFPKASKIKVTMKDGGYYTFELNKKLQT
NRMSDVIDGRNIEKIEANIR″

<u>SEQ ID No:59 - SSL7</u>

<u>gene</u> 129656..130351
/gene="EMRSA 16(252)*ssl7*"
<u>CDS</u> complement 129656..130351
/gene="EMRSA 16(252)*ssl7*
/product="(similar to SET1)SSL7"
/translation="MKLKTLAKATLALGLLTTGVITSEGQAVQAAEKQERVQHLHDIRDLHRYYSSESFEYSNVSG
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NKVNGEDLDASIDSFLIQKEEISLKELDFKIRQQLVNNYGLYKGTSKYGKIIINLKDENKVEIDLGDKLQFERMGD
VLNSKDIRGISVTINQI″

<u>SEQ ID No:60 - SSL9</u>

<u>gene</u> 128617..129315
/gene="EMRSA 16(252)*ssl9*"
<u>CDS</u> complement 128617..129315
/gene="EMRSA 16(252)*ssl9*
/product="(similar to SET5)SSL9"
/translation="MKLTAIAKATLALGILTTGVMTAESQTVNAKVKLDETQRKYYINMLKDYYSQESYESTNISV
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LQVKKVDPKDGFSIKELFFIQKEEVSLKELDFKIRKMLVEKYRLYKGASDKGRIVINMKDEKKHEIDLSEKLSFDR
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<u>SEQ ID No:61 - SSL10</u>

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gene                127571..128254
                    /gene="EMRSA 16(252)ssl10"
     CDS            complement 127571..128254
                    /gene="EMRSA 16(252)ssl10
                    /product="(similar to SET4)SSL10"
/translation="MKLTALAKVTLALGILTTGTLTTEAHSGHAKQNQKSVNKHDKEALHRYYTGNFKEMKNIN
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TKEKGEDAFVKGYPYDIKKEEISLKELDFKLRKHLIEKYGLYKTLSKDGRIKISLKDGSFYNLDLRTKLKFKHMGE
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SEQ ID No:62 - SSL11

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                    /gene="EMRSA 16(252)ssl11"
     CDS            complement 123447..124145
                    /gene="EMRSA 16(252)ssl11
                    /product="(similar to SET15 from strain Mu50)SSL11"
/translation="MKLKNIAKASLALGILTTGMITTTAQPVKASEQSRLSVTSNDTQELKKYYSGTGYNFQNV
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GLEITKPTGHNTATRQAETYRINKEEISLKELDFKLRKHLIENHELYKTEPKDGKIRITMKGGGYYTFELNKKLQP
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SEQ ID No:63

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38500 A CAATGTAAGT TGGGGTGGGG CCCCAACATA GAGAAATTGG GTTACCAATT TCTACAAGCA ATGCAAGTT
38570 G GGGCGGGCCC AAACCCAGAG AATGACTTGG CATTTCTATT AGACTCCAAA TCGCATTTAA TATTCTGTG
38640 T ACTAAATTAA TGATTGTGTA AGTACTATTG AGACATTTTG TAGTATTACT CAAATATTGT TTATCCTTA
38710 G TATTTACGAT ATAAATCATA CGACCTTATT TAATCAATGA GGACTTCGAC TGTTATTTTT TGAGGATTT
38780 T TAACATAAAC ATTTGCAAGA TCAGAATGTA ATCTTTTACT CAAATCAATT GTAAAGTCAT TGCCGCCAC
38850 C GGTGATTTTA AGTTTACCTT TATTGCGATT TTCATGATAT AATATTTTAT TTTTAATTAG TGTTTCACG
38920 T GCTCGAAAAT CAATTTCTTT CAATGTTAAT ATTGGTTTAT TACCTTGGTA CATCTTATGT GCACCAATA
38990 A TTGTTTGTAG TTTATCTTTG TATTGGACAA AAAGACTATA TGGTTTATCA GAAGGTGATG CAGCAGGTG
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SEQ ID No:66 - SSL14

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S. aureus strain MSSA-476 taken from unpublished genome project at the Sanger centre via http://pedant.gsf.de

SEQ ID No:67

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121170 T AAAAGAGCTG GATTATAAGT TGAGAAAGCA TCTAATCGAA AAATATGGAC TTTATAAAAC AATCTCAAA
121240 A GATGGTAGGG TCAAAATTAG CTTGAAAGAT GGCAGTTTTT ATAACCTTGA TTTAAGATCT AAATTAAAA
121310 T TCAAATATAT GGGGGAAGTC ATAGAAAGCA AACAAATTAA AGATATTGAA GTTAACTTAA AGTAAATAA
121380 T TACGAATAAT AAAAAGTAAT TGAAGCGGCT TAACGATGAA AAGTAAATTG ATGCGCATAC CTTACCAAA
121450 A GGATGCATCA ATCGATATCG TCGTTAAGCT GTTTTGGTTT ACGTTTCATG GATTCTACCC CAATTTTCA
121520 T AAATATAAAA ATTCCACCAC CAACATCAAA ATTCTCAACA TCGCAACATA CCCAAATGTT ATAATAAAT
121590 C TATTACACAA AGAGATAAAT TACTTATTCA AAGGCGGAGG AATCACATGT CTATTACTGA AAAACAACG
121660 T CAGCAACAAG CTGAATTACA TAAAAAATTA TGGTCGATTG CGAATGATTT AAGAGGGAAC ATGGATGCG
121730 A GTGAATTCCG TAATTACATT TTAGGCTTGA TTTTCTATCG CTTCTTATCC GAAAAAGCAG AACAAGAAT
121800 A TGCAGATGCG TTGGCAGGTG AAGATATCAC GTATCAAGAG ACATGGGCAG ATGAAGAATA TCGTGAAGA
121870 C TTAAAAGCTG AATTAATTGA TCAAGTCGGT TACTTCATTG AACCACAAGA TTTATTCAGT GCGATGATT
121940 C GTGAAATTGA AACGCAAGAT TTCGATATCG AACATCTGGC GACGGCAATT CGTAAAGTTG AAACATCAA
122010 C ATTAGGTGAA GAAAGTGAAA ATGACTTTAT CGGACTGTTC AGCGATATGG ACTTAAGTTC AACGCGACT
122080 A GGTAACAATG TCAAAGAACG TACTGCTTTA ATCTCTAAAG TCATGGTTAA TCTTGACGAT TTACCATTT
122150 G TTCACAGTGA TATGGAAATT GATATGTTAG GTGATGCATA TGAATTCCTA ATTGGGCGCT TTGCGGCGA
122220 C AGCAGGTAAA AAAGCAGGCG AGTTCTATAC ACCACAACAA GTATCTAAGA TACTGGCGAA GATTGTCAC
122290 A GACGGTAAAG ATAAATTACG TCATGTGTAC GACCCAACAT GTGGTTCCGG TTCATTATTG TTACGTGTT
122360 G GTAAAGAAAC GCAAGTGTAT CGTTATTTCG GTCAAGAACG TAACAATACC ACTTACAACT TAGCACGCA
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122430 T GAACATGTTA TTACATGATG TACGTTATGA AAATTTCGAT ATCCGTAATG ATGACACGTT GGAAAATCC
122500 A GCCTTTTTAG GACATACATT TGATGCGGTT ATTGCGAACC CACCATACAG TGCGAAATGG ACAGCAGAT
122570 T CAAAATTTGA AAATGACGAA CGATTCAGCG GATACGGCAA ACTTGCGCCA AAGTCCAAAG CAGACTTTG
122640 C CTTTATTCAA CACATGGTAC ATTACTTAGA CGATGAAGGT ACCATGGCCG TTGTACTCCC ACATGGTGT
122710 C TTATTCCGTG GTGCTGCAGA AGGTGTCATT CGTCGTTATT TAATTGAAGA AAAGAACTAC TTAGAAGCC
122780 G TGATTGGCTT ACCAGCCAAT ATTTTCTATG GGACAAGTAT TCCAACATGT ATTTTAGTAT TTAAAAAAT
122850 G TCGCCAACAA GAAGACTATG TATTATTTAT CGATGCATCC AATGATTTTG AAAAAGGAAA AAATCAAAA
122920 C CATTTAACCG ATGCCCAAGT CGAACGCATT ATTAACACAT ATAAGCGTAA GGAAACAATT GATAAATAT
122990 A GCTACAGTGC GACATTACAA GAGATCGCCG ATAACGATTA CAACTTAAAC ATACCGAGAT ATGTCGATA
123060 C ATTCGAAGAA GAAGCACCGA TTGATTTAGA TCAAGTCCAA CAAGATTTGA AAAATATCGA CAAAGAAAT
123130 C GCAGAAGTTG AACAAGAAAT CAATGCATAC CTGAAAGAAC TTGGGGTGTT GAAAGATGAG TAATACACA
123200 A AAGAAAAATG TGCCAGAGTT GAGGTTCCCA GGGTTTGAAG GCGAATGGGA AGAGAAGAAG TTAGGGGAC
123270 C TTACTACCAA AATAGGTAGT GGAAAGACTC CCAAAGGTGG AAGTGAAAAC TATACAAACA AAGGCATAC
123340 C ATTTTTAAGG AGTCAAAATA TTAGAAATGG TAAATTAAAT CTTAATGACT TAGTTTATAT TAGTAAAGA
123410 T ATAGATGATG AGATGAAAAA TAGTAGAACG TACTATGGTG ATGTTCTTTT AAATATTACA GGAGCATCA
123480 A TAGGTAGAAC AGCCATTAAT TCGATAGTTG AAATACATGC TAATTTAAAT CAACATGTAT GTATTATTA
123550 G ATTGAAAAAA GAGTATTATT ATAATTTTTT TGGACAGTAT CTATTATCAA GAAAAGGTAA AAGGAAAAT
123620 T TTCCTTGCAC AAAGTGGAGG TAGTCGAGAA GGACTAAACT TCAAAGAAAT TGCTAATTTA AAAATCTTC
123690 A CCCCAACTAT ATTTGAAGAG CAGCAAAAAA TAGGCGAATT CATCAGCAAA CTTGACCGAC AAATTGAAT
123760 T AGAAGAACAA AAACTTGAAT TACTTCAGCA ACAGAAAAAA GGCTATATGC AGAAAATCTT CTCGCAAGA
123830 A TTGCGATTCA AAGATGAGGA AGGTAAAGAT TATCCAGATT GGAAATCAAA ATCAATTCAA GAAATATTT
123900 G AGAATAAGGG TGGCACTGCT CTAGAAACAG AATTTAATTT TGACGGTAAT TATAAAGTTA TAAGTATAG
123970 G AAGTTATTCT ATAAATAGCA CTTATAATGA TCAAAATATA AGAGTCAATA AAAATAAAAA AACTGAAAA
124040 A TATATTTTAT CAAAAGGCGA CTTAGCAATG GTATTAAATG ATAAAACAAA AGATGGGAAA ATTATAGGT
124110 A GAAGTATATT TATAGATAAA GATAATCAAT ATATTTATAA TCAAAGAACT GAAAGATTAA TACCATTTG
124180 C TGAAAATGAT AATAAATTTT TATGGTTCTT AATGAATACA GATTTAATTA GAAATAAAAT AAAAGGTAT
124250 G ATGCAAGGAG CAACCCAAGT TTATATAAAT TATTCATCTA TTAAATTGAT ATCTATACAA TTGCCACTT
124320 C TTGAAGAACA ACAGAAAATA AGAGGGTTTC TAGAAGTTTT ATCTGGAATA ACTACTAAAC AATTGCACA
124390 A GATAGACCAA TTAAAAGAGA GGAAAAAGGC GTTTTTACAG AAAATGTTTA TTTGATTTGT CGCTGCAAT
124460 A TAGTTTTTAT TATTTGTTTA TTTCAGATGT TTCACCATCA TATTGCGTAA CTTTTACAAA TAAGAAATA
124530 A AGTTCAATGA AATCAAAAAC GAACATTAAA TTTAGGCACT GTGATAGCAC AGTGTCTTTT TTGTGTCGA
124600 A ATTGTGTACA GAATAAGTAG TTAAATAAAG ATTAAGTTGA GATAAAGTGT TATTCGTAAA TAAAAGAGA
124670 G TAGATCGATA GGAATTGAAT GATATTAGTT AACTATTTAT TAAATTACTT AATAATGATT AATTTTTAG
124740 T TAAAGTAAGT TTAATGTGAA GCACGACCAT TGCTCATTAT AATGAATGAG GATTGTTCGT ATTGCGTAA
124810 T AGAATAAATC AAATAGACTA AAAATTGGGA GCATAGAATT ATGAAATTAA AAAATATTGC TAAAGCAAG
124880 T TTAGCACTAG GGATTTTAAC AACAGGGATG ATTACAACTA CTGCTCAGCC AGTAAAAGCA ATTGAGCAA
124950 A GCAGATTATC AGTTACTTCA AAAGATACAC AAGAATTAAA AAAATACTAC AGTGGAACAG GATATAATT
125020 T TCAAAATGTG AGTGGTTATA GAGAAGGTAA TAAAATGAAC ATTATTGATG GACCACAACT TAATGTAGT
125090 T ACTTTACTTG GCACAGACAA AGAAAGGTTT AAGGACGATG AAGATTATGA AGGACTTGAT GTATTTGTT
125160 G TAAGAGAAGG GTCAGGTAAA CACGCAGATA ATATATCAAT TGGTGGAATT ACAAAAAACAA ATAAGAATC
125230 A ATATAAAGAC CCTGTACAAA ACGTTAATTT ATTGACTTCT AAGAGTAACG GTCAAAATAC TGCTTCTGT
125300 G ACTTCAGAAT ACTATAGCAT CAATAAAGAA GAAATTTCAT TAAAAGAACT TGATTTCAAA CTAAGAAAG
125370 C AATTAATTGA TAAACATGAT CTTTATAAGA CAGAGCCTAA AGACAGCAAA ATTAAAGTTT CTATGAAAA
125440 A TGGCGGCTAC TATACGTTTG AATTAAATAA AAAATTACAG CCTCATCGCA TGGGTGATAC GATTGATAG
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SEQ ID No:68 - SSL1

gene 110541..111236
/gene=" MSSA-476*ssl1*"
CDS 110541..111236
/gene="MSSA-476*ssl1*
/product="(Similar to SET6 from strain Mu50)SSL1"

/translation="MGLKIMKFKAIAKASLALGMLATGVITSNVQSVQAKTEVKQQSEADLKLYYNGPSFEYKKVTGYGFIEGKDRFIDFIYNGQYNKISLVGSDKDKYNEEVNPDIDVFVVREGNGRQADNHSIGGITKTNRGVYYDYIHTPILEIKKGKEEPQSSLYQIYKEDISLKELDFKLRKQLISQSGLYSNGLKQGQITITMNDGTTHTIDLSQKLEKERMGESIDGRQIQKILVEMK"

SEQ ID No:69 - SSL2

gene 111522..112217
/gene=" MSSA-476*ssl2*"
CDS 111522..112217
/gene="MSSA-476*ssl2*
/product="(Similar to SET7 from strain N315)SSL2"

/translation="MKMKSIVKISLLLGILATGVNTTTEKPVHAEKKPIVISENSKKLKAYYTQPSIEYKNVTGYISFIQPSIKFMNIIDGNSVNNIALIGKDKQHYHTGVHRNLNIFYVNEDKRFEGAKYSIGGITSANDKAVDLIAEARV

IKADHIGEYDYDFFPFKIDKEAMSLKEIDFKLRKYLIDNYGLYGEMSTGKITVKKKYYGKYTFELDKKLQEDRMSD
VINVTDIDRIEIKVRKA"

<u>SEQ ID No:70 - SSL3</u>

<u>gene</u> 112508..113578
/gene=" MSSA-476*ss3*"
<u>CDS</u> 112508..113578
/gene="MSSA-476*ssl3*
/product="(Similar to SET8 from strain Mu50)SSL3"

/translation="MKMRTITKTSLALGLLTTGAITVTTQSVKAEKIQSTKVDKVPTLKAERLAMINITAGANSAT
TQAANTRQERTPKLEKAPNTNEEKTSASKIEKISQPKQEEQKTLNISATPAPKQEQSQTTTESTTQQTKMTTPPST
NTPQPMQSTKSDTPQSPTIKQAQTDMTPKYEDLRAYYTKPSFEFEKQFGFLLKPWTTVRFMNVIPNRFIYKIALVG
KDEKKYKDGPYDNIDVFIVLEDNKYQLKKYSVGGITKTNSKKVNHKVELSITKKDNQGMISRDVSEYMITKEEISL
KELDFKLRKQLIEKHNLYGNMGSGTIVIKMKNGGKYTFELHKKLQEHRMADVIDGTNIDNIEVNIK"

<u>SEQ ID No:71 - SSL4</u>

<u>gene</u> 113943..114890
/gene=" MSSA-476*ssl4*"
<u>CDS</u> 113943..114890
/gene="MSSA-476*ssl4*
/product="(Similar to SET9 from strain N315)SSL4"
/translation="MKITTIAKTSLALGLLTTGVITTTTQAANATTPPSTKVETPQQVANATTPSSTKVEAPQQAA
NATTPSSTKVEAPQSKPNATTPSSTKVEAPQQAANATTPPSSNVDTSPPQSPTTKQVPTEINPKFKDLRAYYTKPS
LEFKNEIGIILKKWTTIRFMNVVPDYFIYKIALVGKDDKKYGEGVHRNVDVFVVLEENNYNLEKYSVGGITKSNSK
KVDHKAGVRITKEDNKGTISHDVSEFKITKEQISLKELDFKLRKQLIEKNNLYGNVGSGKIVIKMKNGGKYTFELH
KKLQENRMADVIDGTNIDNIEVNIK"

<u>SEQ ID No:72 - SSL5</u>

<u>gene</u> 115254..115958
/gene=" MSSA-476*ssl5*"
<u>CDS</u> 115254..115958
/gene="MSSA-476*ssl5*
/product="(Similar to SET10 from strain Mu50)SSL5"
/translation="MKMAAIAKASLALGILATGTITSLHQTVNASEHEAKYENVTKDIFDLRDY
YSGASKELKNVTGYRYSKGGKHYLIFDKHQKFTRIQIFGKDIERFKARKNPGLDIFVVKEAENRNGTVFSYGGVTK
KNQDAYYDYINAPRFQIKRDEGDGIATYGRVHYIYKEEISLKELDFKLRQYLIQNFDLYKKFPKDSKIKVIMKDGG
YYTFELNKKLQTNRMSDVIDGRNIEKIEANIR"

<u>SEQ ID No:73 - SSL6</u>
<u>gene</u> 116404..117102
/gene=" MSSA-476*ssl6*"
<u>CDS</u> 116404..117102
/gene="MSSA-476*ssl6*
/product="(Similar to SET2 from strain NCTC6571)SSL6"

/translation="MKLKALAKATLVLGLLATGVITTESQTVKAAESTQGQHNYKSLKYYYSKPSIELINVDGLYR
QHLTDKGAYVWKNLKDYYIGLLGEDSKKFKSDVYGDLDAFLVIEEEPVKGRQYSIGGISKTNSKEFKEREVDVKVT
RKADRDTTSTKDSKFKITKEEISLKELDFKLRQKLMKEENLYDAINHRKGKIVVKMEDDKFYTFELTKKLQPHRMG
DTIDGTKIKEINVELEYK"

<u>SEQ ID No:74 - SSL7</u>

<u>gene</u> 117524..118219
/gene=" MSSA-476*ssl7*"
<u>CDS</u> 117524..118219
/gene="MSSA-476*ssl7*
/product="(Similar to SET1-C)SSL7"

/translation="MKLKTLAKATLALGLLTTGVITSEGQAVQAKEKQERVQHLYDIKDLHRYYSSESFEFSNISG
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KKVYGGNLDASIESFLINKEEVSLKELDFKIRQHLVKNYGLYKGTTKYGKITFNLKDGEKQEIDLGDKLQFEHMGD
VLNSKDIQNIAVTINQI"

<u>SEQ ID No:75 - SSL8</u>

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    gene            118558..119256
                    /gene=" MSSA-476ssl8"
    CDS             118558..119256
                    /gene="MSSA-476ssl8
                    /product="(Similar to SET12 from strain Mu50)SSL8"
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/translation="MKFTAIAKAIFVLGILTTSVMITENQSVNAKGKYEKMNRLYDTNKLHQYYSGPSYELTNVSG
QSQGYYDSNVLLFNQQNQKFQVFLLGKDENKYKEKTHGLDVFAVPELVDLDGRIFSVSGVTKKNVKSIFESLRTPN
LLVKKIDDKDGFSYDEFFFIQKEEVSLKELDFKIRKLLIKKYKLYEGAADKGRIVINMKDENKYEIDLSDKLGFER
MADVINSEQIKNIEVNLK"

<u>SEQ ID No:76 - SSL9</u>

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    gene            119635..120333
                    /gene=" MSSA-476ssl9"
    CDS             119635..120333
                    /gene="MSSA-476ssl9
                    /product="(Similar to SET13 from strain Mu50)SSL9"
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/translation="MKFTALAKATLALGILTTGVFTTESKAVHAKVELDETQRKYYINMLHQYYSEESFEPTNISV
KSEDYYGSNVLNFKQRNKAFKVFLLGDDKNKYKEKTHGLDVFAVPELIDIKGGIYSVGGITKKNVRSVFGFVSNPS
LQVKKIDPKHGFSINELFFIQKEEVSLKELDFKIRKMLVEKYRLYKGASDKGRIVINMKDEKKYVIDLSEKLSFDR
MFDVMDSKQIKNIEVNLN"

<u>SEQ ID No:77 - SSL10</u>

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    gene            120692..121375
                    /gene=" MSSA-476ssl10"
    CDS             120692..121375
                    /gene="MSSA-476ssl10
                    /product="(Similar to SET14 from strain Mu50)SSL10"
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/translation="MKLTAIAKAALALGILTTGTLTTEVHSGHAKQNQKSVNKHDKEALYRYYTGKTMEMKNISAL
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EKGEDAFVKGYPYYIKKEKITLKELDYKLRKHLIEKYGLYKTISKDGRVKISLKDGSFYNLDLRSKLKFKYMGEVI
ESKQIKDIEVNLK"

<u>SEQ ID No:78 - SSL11</u>

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    gene            124851..125543
                    /gene=" MSSA-476ssl11"
    CDS             124851..125543
                    /gene="MSSA-476ssl11
                    /product="(Similar to SET15 from strain Mu50)SSL11"
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/translation="MKLKNIAKASLALGILTTGMITTTAQPVKAIEQSRLSVTSKDTQELKKYYSGTGYNFQNVSG
YREGNKMNIIDGPQLNVVTLLGTDKERFKDDEDYEGLDVFVVREGSGKHADNISIGGITKTNKNQYKDPVQNVNLL
TSKSNGQNTASVTSEYYSINKEEISLKELDFKLRKQLIDKHDLYKTEPKDSKIKVSMKNGGYYTFELNKKLQPHRM
GDTIDSRNIKKIEVNL"

<u>SEQ ID No:79</u>

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62000 C CTAAATTGTA AGCGCATACA AAATAAACAC AACCTACTAT TAAAATTTGT AATATTTTAT CAATAATTA
62070 A ATGAACATTT TATTAATATT AAATTTAAGT AGTAGGAAAT AATTAAAATA AGTACTACAT TTAAAGTAT
62140 A ACTATTTTTC AAGTAGTTAG AAAATTCAAT TATCAAACAA TTTAATGCAA TTGATTAGAG AATAATTGT
62210 A ACGTGTCGTT TTTAATATAT AACTCCCGCC TACTTTATTA AGTACTGTTT CTGTCCAAAA CTTAAAAAT
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62280 G ATAAGTTTTG CTTAAATAAC ACTACTAACT GTTTAAGTTT ATTTAACATA GTTTTAGCTT TTATTTAAT
62350 T CCGAATCGGT GTAATAGCTT ATATACTTTG GGTAATTCAC GCAAAGGAGA TTTTCATATG AAAAAGAAC
62420 A TCATGAATAA ATTAGTTTTA TCAACAGCAT TGTTACTTTT AGGAACTACA TCAACACAAC TTCCTAAAA
62490 C ACCAATCAGT TTTTCATCTG AAGCAAAAGC CTATAATATC AGTGAAAACG AGACTAATAT CAATGAGTT
62560 A ATAAAGTATT ATACACAGCC TCATTTATCA CTATCAAATA AATGGTTATG GCAAAAGCCC AATGGTAGC
62630 A TTCATGCAAC ATTGCAAACG TGGGTTTGGT ATAGTCATAT TCAAGTGTTT GGATCCGAGA GTTGGGGAA
62700 A CATTAATCAG TTAAGAAATA AATACGTTGA TATATTTGGA ACTAAAGATG AGGACACAGT TGAAGGTTA
62770 C TGGACTTATG ATGAAACATT TACTGGTGGT GTTACGCCAG CAGCTACTTC ATCTGATAAG CCTTATAGA
62840 C TATTTTTAAA ATATAGTGAT AAACAACAAA CTATCATCGG TGGACATGAA TTTTACAAAG GAAATAAAC
62910 C AGTATTAACT TTAAAAGAAT TAGATTTCCG TATTCGTCAA ACATTAATAA AAAATAAAAA GTTATATAA
62980 C GGAGAATTTA ATAAAGGTCA AATTAAGATA ACTGCTGATG GAAATAATTA CACGATTGAT TTAAGTAAA
63050 A AGTTAAAATT AACTGACACA AACCGTTATG TTAAAAATCC TAAAAATGCA CAAATTGAAG TCATACTCG
63120 A AAAATCTAAC TaACCTATTA CCTTTTGTAA ATGCGGATAa TTTCAAttaT CTAATTAaCC CCTTTTATA
63190 A TTAAACATTC CAacaaTACT CAAAGGAGaa AttCGAATga acAATaacaT CaCGaAAAAA ATTATTTTA
63260 T CaaCAACATT GTTACTATTA GGTACAGCAT CTACACAATT TCCTAATACA CCTATCAATT CTTCATCTG
63330 A AGCGAAAGCT TATTATATAA ATCAAAACGA AACTAACGTT AATGAGTTAA CTAAATATTA CTCGCAAAA
63400 A TATTTAACCT TCTCTAACAG TACGTTATGG CAAAAAGATA ACGGTACGAT TCATGCAACG TTGTTACAG
63470 T TTTCTTGGTA TAGTCATATT CAAGTTTATG GACCTGAAAG TTGGGGCAAT ATCAACCAAT TAAGAAATA
63540 A AAGCGTTGAT ATTTTTGGCA TAAAAGACCA AGAAACCATT GATTCTTTTG CATTATCTCA AGAAACGTT
63610 T ACTGGTGGTG TTACTCCTGC AGCAACATCT AACGATAAAC ACTATAAACT GAATGTGACA TATAAAGAT
63680 A AAGCAGAAAC GTTTACTGGC GGATTTCCAG TTTATGAAGG CAATAAGCCT GTTTTAACTT TAAAAGAAT
63750 T AGATTTTCGT ATTCGTCAAA CATTAATTAA AAGTAAAAAA TTATATAATA ATTCTTATAA TAAAGGACA
63820 A ATTAAAATAA CAGGTGCAGA CAATAACTAC ACAATAGATT TAAGTAAAAG GTTGCCATCA ACTGATGCA
63890 A ATAGATATGT TAAAAAACCT CAAAATGCAA AAATTGAAGT TATCCTCGAA AAATCAAACT AACAATAAT
63960 A ATGGAGTTAA TAAAAATAAT CGCAAATACT ATATTGACTT CGCTCACATT TAAATTTCTT ATTCCTCGT
64030 A TCATGATTCC TCTGAAAGGA GATGTTCTAA TGAGTAAGAA CATCACGAAA AATATAATTT TAACGACAA
64100 C ATTATTACTA TTAGGTACTG TATTACCTCA AAATCAAAAA CCAGTATTTA GTTTTTACTC TGAAGCTAA
64170 A GCTTATAGCA TTGGTCAAGA TGAAACTAAC ATCAATGAAT TAATTAAATA TTACACACAG CCTCATTTT
64240 T CATTTTCAAA TAAATGGCTA TATCAATATG ATAATGGAAA CATTTATGTT GAACTTAAGA GATATTCAT
64310 G GTCAGCACAT ATATCTTTAT GGGGCGCTGA AAGTTGGGGA AATATTAATC AGTTAAAAGG TCGTTACGT
64380 A GATGTGTTTG GACTAAAAGA CAAAGATACT GATCAGTTAT GGTGGTCTTA TAGAGAGACA TTTACAGGT
64450 G GCGTTACACC AGCCGCAAAA CCTTCTGATA AAACTTATAA TCTTTTTGTG CAATACAAAG ATAAACTAC
64520 A AACGATTATT GGTGCGCATA AAATATACCA AGGCAATAAA CCAGTATTAA CATTGAAAGA AATCGATTT
64590 C CGTGCACGAG AAGCGTTAAT AAAAAATAAA ATATTATATA ACGAAAATCG TAATAAAGGT AAGCTTAAG
64660 A TCACCGGTGG CGGTAATAAC TACACTATTG ATTTAAGCAA AAGATTACAT TCAGATCTAG CAAATGTTT
64730 A TGTTAAAAAT CCTAATAAAA TAACTGTTGA CGTCCTCTTT GATTAGTATA TGAAGGTGAC TTATACTTC
64800 A TGCACTTTAA TTCCAAATCA GATTATTTAA ATGATAATTT TTAAAGTGTA TGATGTATAT AATAGGTAA
64870 A ATTTTCTATA TATTTAAATG GAATTGGGAG TAGGAATGTG ACAGAAATAG TATTTTATAA AATTTATTT
64940 C GTTGTCACTC CCCAACTTGC ATTGTCTGTA GAATTTCTTT TTGAAATTCT CTATGTTGGG GCCCCGCCA
65010 A CTTGCACATT ATTGTAAGCT GACTTTTCGT CAGCTTCTGT GTTGGGGCCC CGCCTATAAT TGAAAAATG
65080 C TTGTTACATG GGCATTTTCA TTCGGTCAAC TACTACCAAT ATAATATTGT AGAGCCTAAG ACATTGATT
65150 T ATTATGTCTT AGGCTCTATT CCTTCATTTA ATGATTCAAT TATTATAGCA ATACTTTATT GTCCCATGA
65220 T TAGTGTTCTT TTAATGAGAC ATAGTAACTA TAAAGTTTAA TAATCGTTCT AAATCTAGCA TCTTCTAGT
65290 T TGGTTTTCCC ATTTCTTAAA TCTTGTACTG TTTGATATGG AACTCCTGAA TTTTTCGAAA TTTTATAGC
65360 C TGATTCAGAC TCAAaCAAAG ATTGAAGAGA GTTTATAATA TTATTCAACT CTGTCATTTT TAATCCCCT
65430 T TCTTGAATTA ACAATATATA ATGTTGTTAT TAAAACAGTC AGTGTATGGA TGATTTCATT TCCTAAAAA
65500 T
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SEQ ID No:80 - SSL12

gene 62408..63133
/gene=" MSSA-476*ssl12*"
CDS 62408..63133
/gene="MSSA-476*ssl12*
/product="(Similar to SAV1168 from strain Mu50)SSL12"

/translation="MKKNIMNKLVLSTALLLLGTTSTQLPKTPISFSSEAKAYNISENETNINELIKYYTQPHLSLSNKWLWQKPNGSIHATLQTWVWYSHIQVFGSESWGNINQLRNKYVDIFGTKDEDTVEGYWTYDETFTGGVTPAATSSDKPYRLFLKYSDKQQTIIGGHEFYKGNKPVLTLKELDFRIRQTLIKNKKLYNGEFNKGQIKITADGNNYTIDLSKKLKLTDTNRYVKNPKNAQIEVILEKSN"

SEQ ID No:81 - SSL13

gene 63227..63952
/gene=" MSSA-476*ssl13*"
CDS 63227..63952
/gene="MSSA-476*ssl13*
/product="(Similar to SA1010 from strain N315)SSL13"

/translation="MNNNITKKIILSTTLLLLGTASTQFPNTPINSSSEAKAYYINQNETNVNELTKYYSQKYLTF
SNSTLWQKDNGTIHATLLQFSWYSHIQVYGPESWGNINQLRNKSVDIFGIKDQETIDSFALSQETFTGGVTPAATS
NDKHYKLNVTYKDKAETFTGGFPVYEGNKPVLTLKELDFRIRQTLIKSKKLYNNSYNKGQIKITGADNNYTIDLSK
RLPSTDANRYVKKPQNAKIEVILEKSN"

SEQ ID No:82 - SSL14

gene 64060..64776
/gene=" MSSA-476*ssl14*"
CDS 64060..64776
/gene="MSSA-476*ssl14*
/product="(Similar to SAV1166 from strain Mu50)SSL14"

/translation="MSKNITKNIILTTTLLLLGTVLPQNQKPVFSFYSEAKAYSIGQDETNINELIKYYTQPHFSF
SNKWLYQYDNGNIYVELKRYSWSAHISLWGAESWGNINQLKGRYVDVFGLKDKDTDQLWWSYRETFTGGVTPAAKP
SDKTYNLFVQYKDKLQTIIGAHKIYQGNKPVLTLKEIDFRAREALIKNKILYNENRNKGKLKITGGGNNYTIDLSK
RLHSDLANVYVKNPNKITVDVLFD"

S. aureus strain COL taken from unpublished genome project at The Institute for Genomic Research (TIGR) via ViroloGenome

SEQ ID No:83

ATGAAATTTAAAGCGATAGCAAAAGCAAGTTTAGCATTGGGAATGTTAGCAACAGGTGTAATTACATCGAATGTACAATCAGTAC
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SEQ ID No:84 - SSL1

gene 1..681
/gene=" COL*ssl1*"
CDS 1..681
/gene="COL*ssl1*
/product="(Similar to SET6 from strain N315)SSL1"

/translation="MKFKAIAKASLALGMLATGVITSNVQSVQAKAEVKQQSESELKHYYNKPILERKNVTGFKYT
DEGKHYLEVTVGQQHSRITLLGSDKDKFKDGENSNIDVFILREGDSRQATNYSIGGVTKSNSVQYIDYINTPILEI
KKDNEDVLKDFYYISKEDISLKELDYRLRERAIKQHGLYSNGLKQGQITITMNDGTTHTIDLSQKLEKERMGESID
GTKINKILVEMK"

SEQ ID No:85

ATGAAATTAAAAAATATTGCTAAAGCAAGTTTAGCACTAGGGATTTTAACAACAGGGATGATTACAACTACTGCTC
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SEQ ID No:86 - SSL2

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gene                    1..678
                        /gene=" COLssl2"
     CDS                1..678
                        /gene="COLssl2
                        /product="(Similar to SET7 from strain N315)SSL2"
/translation="MKMKNIAKISLLLGILATGVNTTTEKPVHAEKKPIVISENSKKLKAYYNQPSIEYKNVTGYI
SFIQPSIKFMNIIDGNSVNNIALIGKDKQHYHTGVHRNLNIFYVNEDKRFEGAKYSIGGITSANDKAVDLIAEARV
IKEDHTGEYDYDFFPFKIDKEAMSLKEIDFKLRKYLIDNYGLYGEMSTGKITVKKKYYGKYTFELDKKLQEDRMSD
VINVTDIDRIEIKVIKA"
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SEQ ID No:87

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SEQ ID No:88 - SSL3

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gene                    1..1059
                        /gene=" COLssl3"
     CDS                1..1059
                        /gene="COLssl3
                        /product="(Similar to SET8 from strain N315)SSL2"

/translation="MKMRTIAKTSLALGLLTTGAITVTTQSVKAEKIQSTKVDKVPTLKAERLAMINITAGANSAT
TQAANTRQERTPKLEKAPNTNEEKTSASKIEKISQPKQEEQKTLNISATPAPKQEQSQTTTESTTPKTKVTTPPST
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SEQ ID No:89

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SEQ ID No:90 - SSL4

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gene                    1..924
                        /gene=" COLssl4"
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CDS 1..924
/gene="COL*ssl4*
/product="(Similar to SET9 from strain N315)SSL2"

/translation="MKITTIAKTSLALGLLTTGVITTTTQAANATTPSSTKVEAPQSTPPSTKIEAPQSKPNATTP PSTKVEAPQQTANATTPPSTKVTTPPSTNTPQPMQSTKSDTPQSPTTKQVPTEINPKFKDLRAYYTKPSLEFKNEI GIILKKWTTIRFMNVVPDYFIYKIALVGKDDKKYGEGVHRNVDVFVVLEENNYNLEKYSVGGITKSNSKKVDHKAG VRITKEDNKGTISHDVSEFKITKEQISLKELDFKLRKQLIEKNNLYGNVGSGKIVIKMKNGGKYTFELHKKLQENR MADVINSEQIKNIEVNLK"

SEQ ID No:91

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SEQ ID No:92 - SSL9

gene 1..696
/gene=" COL*ssl9*"
CDS 1..696
/gene="COL*ssl9*"
/product="(Similar to SET13 from strain N315)SSL9"

/translation="MKLTTIAKATLALGILTTGVFTAESQTGHAKVELDETQRKYYINMLHQYYSEESFEPTNISV KSEDYYGSNVLNFKQRNKAFKVFLLGDDKNKYKEKTHGLDVFAVPELIDIKGGIYSVGGITKKNVRSVFGFVSNPS LQVKKVDAKNGFSINELFFIQKEEVSLKELDFKIRKLLIEKYRLYKGTSDKGRIVINMKDEKKHEIDLSEKLSFER MFDVMDSKQIKNIEVNLN"

SEQ ID No:93

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SEQ ID No:94 - SLL10

gene 1..681
/gene=" COL*ssl10*"
CDS 1..681
/gene="COL*ssl10*"
/product="(Similar to SET14 from strain N315)SSL10"

/translation="MKFTALAKATLALGILTTGTLTTEVHSGHAKQNQKSVNKHDKEALYRYYTGKTMEMKNISAL KHGKNNLRFKFRGIKIQVLLPGNDKSKFQQRSYEGLDVFFVQEKRDKHDIFYTVGGVIQNNKTSGVVSAPILNISK EKGEDAFVKGYPYYIKKEKITLKELDYKLRKHLIEKYGLYKTISKDGRVKISLKDGSFYNLDLRSKLKFKYMGEVI ESKQIKDIEVNLK"

SEQ ID No:95

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SEQ ID No:96 - SSL11

gene 1..675
/gene=" COL*ssl11*"
CDS 1..675
/gene="COL*ssl11*"
/product="(Similar to SET15 from strain N315)SSL11"

/translation="MKLKNIAKASLALGILTTGMITTTAQPVKASTLEVRSQATQDLSEYYNRPFFEYTNQSGYKE
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DSVTSTSTSSTYTINKEEISLKELDFKLRKHLIDKHNLYKTEPKDSKIRITMKDGGFYTFELNKKLQTHRMGDVID
GRNIEKIEVNL"

SEQ ID No:97

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SEQ ID No:98 – SSL12

gene 1..723
/gene=" COL*ssl12*"
CDS 1..723
/gene="COL*ssl12*
/product="(similar to SA1011)SSL12"
/translation="MKKNIMNKLVLSTALLLLETTSTQLPKTPISFSSEAKAYNISENETNINELIKYYTQPHF
SLSGKWLWQKPNGSIHATLQTWVWYSHIQVFGSESWGNINQLRNKYVDIFGTKDEDTVEGYWTYDETFTGGVTPAA
TSSDKPYRLFLKYSDKQQTIIGGHEFYKGNKPVLTLKELDFRIRQTLIKNKKLYNGEFNKGQIKITADGNNYTIDL
SKKLKLTDTNRYVKNPRNAEIEVILEKSN"

SEQ ID No:99

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SEQ ID No:100 - SSL13

gene 1048124.. 1048849
/gene=" COL*ss13*"
CDS 1048124.. 1048849
/gene="COL*ssl13*
/product="(similar to SA1010 from strain N315)SSL13"
/translation="MNNNITKKIILSTTLLLLGTASTQFPNTPINSSSEAKAYYINQNETNVNELTKYYSQKYL
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SEQ ID No:101

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SEQ ID No:102 - SSL14

gene 714.. 714
/gene=" COL*ss14*"
CDS 714.. 714
/gene="COL*ssl14*
/product="(similar to SA1009 from strain N315)SSL14"
/translation="MSKNITKNIILTTTLLLLGTVLPQNQKPVFSFYSEAKAYSIGQDETNINELIKYYTQPHF
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KPSDKTYNLFVQYKDKLQTIIGAHKIYQGNKPVLTLKEIDFRAREALIKNKILYNENRNKGKLKITGGGNNYTIDL
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SEQ ID No: 103

***S. aureus* strain N315 (SSL12-SSL14) -coding strand**

1	CTACTGTTCT	TTGTGAAAAA	CCACGGTATT	CAATGCCATC	ATACATTCCA	CCAAGCACAC
61	GTGCAGTATC	TTTAGTTGTT	TCTTTTTTAC	CCATTTGTGA	TCCAGTTGGG	CCTAAATAAG
121	TTACATTTGC	ACCTTGATCA	TGCGCTGCAA	CTTCAAATGC	ACATCGCGTT	CTTGTAGAAT
181	CTTTTTCAAA	TAACAGTGCA	ATATTTTTAT	TTTTTAACAT	AGGCTTTTCA	GTGCCAATAT
241	ATTTAGCACG	TTTTAAATCC	TCGGAGAGTG	TTAATAAGAA	TTCTACCTCT	TGTCGTGAAA
301	AGTCTAATAA	AGTTAAAAAA	CTTCTGTTTC	GTAAATTTTT	CATTAATAAC	AACTCCTTTT
361	ATTTTAGTTA	CACCTAAATT	GTAAGCGCAT	ACAAAATAAA	CACAACCTAC	TATTAAAATT
421	TGTAATATTT	TATCAATAAT	TAAATGAACA	TTTTATTAAT	ATTAAATTTA	AGTAGTAGGA
481	AATAATTAAA	ATAAGTACTA	CATTTAAAGT	ATAACTATTT	TTCAAGTAGT	TAGAAAATTC
541	AATTATCAAA	CAATTTAATG	CAATTGATTA	GAGAATAATT	GTAACGTGTC	GTTTTTAATA
601	TATAACTCCC	GCCTACTTTA	TTAAGTACTG	TTTCTGTCCA	AAACTTAAAA	ATGATAAGTT
661	TTGCTTAAAT	AACACTACTA	ACTGTTTAAG	TTTATTTAAC	ATAGTTTTAG	CTTTTATTTA
721	ATTCCGAATC	GGTGTAATAG	CTTATATACT	TTGGGTAATT	CACGCAAAGG	AGATTTTCAT
781	ATGAAAAAGA	ACATCATGAA	TAAATTAGTT	TTATCAACAG	CATTGTTACT	TTTAGGAACC
841	ACATCAACAC	AACTTCCTAA	AACACCAATC	AGTTTTTCAT	CTGAAGCAAA	AGCCTATAAT
901	ATCAGTGAAA	ACGAGACTAA	TATCAATGAG	TTAATCAAAT	ATTACACTCA	GCCGCATTTT
961	TCATTATCTG	GAAAATGGCT	ATGGCAAAAG	CCCAATGGTA	GCATTCATGC	AACATTGCAA
1021	ACGTGGGTTT	GGTATAGTCA	TATTCAAGTG	TTTGGATCCG	AGAGTTGGGG	AAACATTAAT

1081 CAGTTAAGAA ATAAATACGT TGATATATTT GGAACTAAAG ATGAGGACAC AGTTGAAGGT
1141 TACTGGACTT ATGATGAAAC ATTTACTGGT GGTGTTACGC CAGCAGCTAC TTCATCTGAT
1201 AAACCTTATA GACTATTTTT AAAATATAGT GATAAACAAC AAACTATCAT CGGTGGACAT
1261 GAATTTTACA AAGGAAATAA ACCAGTATTA ACTTTAAAAG AATTAGATTT CCGTATTCGT
1321 CAAACATTAA TAAAGAATAA AAAGTTATAT AACGGAGAAT TTAATAAAGG TCAAATTAAG
1381 ATAACTGCTG ATGGAAATAA TTACACGATT GATTTAAGTA AAAAGTTAAA ATTAACTGAC
1441 ACAAACCGTT ATGTTAAAAA TCCTAAAAAT GCACAAATTG AAGTCATACT CGAAAAATCT
1501 AACTAACCTA TTACCTTTTG TAAATGCGGA TAATTTCAAT TATCTAATTA ACCCCTTTTT
1561 ATAATTAAAC ATTCCAACAA TACTCAAAGG AGAAATTCGA ATGAACAATA ACATCACGAA
1621 AAAAATTATT TTATCAACAA CATTGTTACT ATTAGGTACA GCATTTACAC AATTTCCTAA
1681 TACACCTATC AATTCTTCAT CTGAAGCGAA AGCTTATTAT ATAAATCAAA ACGAAACTAA
1741 CGTTAATGAG TTAACTAAAT ATTACTCGCA AAAATATTTA ACCTTCTCTA ACAGTACGTT
1801 ATGGCAAAAA GATAACGGTA CGATTCATGC AACGTTGTTA CAGTTTTCTT GGTATAGTCA
1861 TATTCAAGTT TATGGACCTG AAAGTTGGGG CAATATCAAC CAATTAAGAA ATAAAAGCGT
1921 TGATATTTTT GGCATAAAAG ACCAAGAAAC CATTGATTCT TTTGCATTAT CTCAAGAAAC
1981 GTTTACTGGT GGTGTTACTC CTGCAGCAAC ATCTAACGAT AAACACTATA AACTGAATGT
2041 AACATATAAA GATAAAGCAG AAACGTTTAC TGGCGGATTT CCAGTTTATG AAGGCAATAA
2101 GCCTGTTTTA ACTTTAAAAG AATTAGATTT TCGTATTCGT CAAACATTAA TTAAAAGTAA
2161 AAAATTATAT AATAATTCTT ATAATAAAGG ACAAATTAAA ATAACAGGTA CAGACAATAA
2221 CTACACAATA GATTTAAGTA AAAGGTTGCC ATCAACTGAT GCAAATAGAT ATGTTAAAAA
2281 ACCTCAAAAT GCAAAAAATTG AAGTTATCCT CGAAAAATCA AACTAACAAT AATAATGGAG
2341 TTAATAAAAA TAATCGCAAA TACTATATTG ACTTCGCTCA CATTTAAATT TCTTATTCCT
2401 CGTATCATGA TTCCTCTGAA AGGAGATGTT CTAATGAGTA AGAACATCAC GAAAAATATA
2461 ATTTTAACGA CAACATTATT ACTATTAGGT ACTGTATTAC CTCAAAATCA AAAACCAGTA
2521 TTTAGTTTTT ACTCTGAAGC TAAAGCTTAT AGCATTGGTC AAGATGAAAC TAACATCAAT
2581 GAATTAATTA AATATTACAC ACAGCCTCAT TTTTCATTTT CAAATAAATG GCTATATCAA
2641 TATGATAATG GAAACATTTA TGTTGAACTT AAGAGATATT CATGGTCAGC ACATATATCT
2701 TTATGGGGCG CTGAAAGTTG GGGAAATATT AATCAGTTAA AAGATCGTTA CGTAGATGTG
2761 TTTGGACTAA AAGACAAAGA TACTGATCAG TTATGGTGGT CTTATAGAGA GACATTTACA
2821 GGTGGCGTTA CACCAGCCGC AAAACCTTCT GATAAAACTT ATAATCTTTT TGTGCAATAC
2881 AAAGATAAAC TACAAACGAT TATTGGTGCG CATAAAATAT ACCAAGGCAA TAAACCAGTA
2941 TTAACATTGA AAGAAATCGA TTTCCGTGCA CGAGAAGCGT TAATAAAAAA TAAAATATTA
3001 TATACCGAAA ATCGTAATAA AGGTAAGCTT AAGATCACCG GTGGCGGTAA TAACTACACT
3061 ATTGATTTAA GCAAAAGATT ACATTCAGAT CTAGCAAATG TTTATGTTAA AAATCCTAAT
3121 AAAATAACTG TTGACGTCCT CTTTGATTAG TATATGAAGG TGACTTATAC TTCATGCACT

SEQ ID No. 104

S. aureus **strain NCTC8325 (SSL1-SSL11) – coding strand**

1 TTGATTAAAA TAATCTAATT GTCGAACAGG AACTTTTCCG CGCCAATCTT CTGGAACTTT
61 CTCAACATTT CTAACACCAA TGTGAAAATG ATCTATGTGA TTTGCAATGG CTTGATTTGT
121 AATATGTGTG CCTAAATGAC CTGTAGCACC TGTTAACATA ATATTCATTC ACTTCATCTC
181 CTAATCTTTA TATACATAAC ATAATACTTA TTTGATGGTT TTCAAAACAT TTGATTTTAT
241 AAAAAATTCT AATCTGTATT TATTGTCGAC GTGTATAGTA AATACGTAAA TATTATTAAT
301 GTTGAAAATG CCGTAATGAC GCGTTTTAGT TGATGTGTAT CACTAATATC ATTGAAAATT
361 TTAATCAGGT ACTACGACAA TATGATGTCT GTTTTGTGTC TGAAAGTTTT ACAGTTTTTA
421 AAATAAAAAT GGTATAAAGT GTGATTTGTA TAAAAAAGAG TCTCGACGGA TAAGAATTGA
481 TTAATAACAG TTAGCATTTT ATTAATTACC TTAACAATGA TTCAAGTTTA GTTAAATGAG
541 GTTTAATTTG AAAGGGGATA GCGCCTCAAT ATAATGTAGG TAGATTGTTC ATATTACGTA
601 ATTGAAAAAT CAAATTTAAA TAGATTGGGG CTAAAAAATTA TGAAATTTAA AGCGATAGCA
661 AAAGCAAGTT TAGCATTGGG AATGTTAGCA ACAGGTGTAA TTACATCGAA TGTACAATCA
721 GTACAAGCGA AAGCAGAAGT TAAACAACAA AGTGAATCAG AGTTAAAACA CTATTATAAT
781 AAACCAATTT TAGAGCGTAA AAATGTGACT GGATTTAAAT ATACTGATGA GGGTAAACAC
841 TATTTAGAAG TCACAGTAGG GCAACAGCAT TCTCGAATCA CTTTACTTGG ATCTGATAAA
901 GATAAATTTA AAGACGGAGA AAACTCAAAT ATAGATGTGT TTATCCTTAG AGAAGGTGAC
961 AGTAGACAAG CAACAAATTA CTCAATTGGT GGCGTTACAA AATCAAATAG TGTGCAGTAT
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15481	GGTGATGTTA	TTGATGGCAG	AAATATAGAA	AAAATTGAAG	TGAATTTATA	AAATTATTCG
15541	AGGGAGCATA	TCATGAGGGA	AAATTTTAAG	TTACGTAAAA	TGAAAGTCGG	TTTAGTATCT
15601	GTTGCAATTA	CAATGTTATA	TATTATGACA	AACGGACAAG	CAGAAGCATC	TGAAAATCAA
15661	AACGCTTTAA	TCTCTAATAT	AAATGTAGAC	AATCAG		

SEQ ID No. 105

S. aureus **strain EMRSA 16(252) (SSL1-SSL11) –coding strand**

1	TGCAATGGCT	TGATTTGTAA	TATGTGTGCC	TAAATGACCT	GTAGCACCTG	TTAACATAAT
61	ATTCATTCAC	TTCATCTCCT	AATCTTTATA	TACATAACAT	AATACTTATT	CGATGATTTT
121	CAAAACATTT	GATTTTATAA	AAAATTGCAA	TCTGTATTTA	TTGTCGCCGT	GTATAGTAAA
181	TACGCATATG	TTATTAATGT	TAAAAATACC	GTAATGACGC	GTTTTAGTTG	ATGCGTGTCA
241	CCATGATCTT	TGAAAATTTT	GACATGGTAC	TGCGACGATA	TGATGTCATT	TTTGTGTCTG
301	AAAGTTTTAC	AGTTTTTAAA	ATTAAAATGG	TTTAAAGTGT	GAATTGTATA	AAAAAGAGTC
361	TTGACGGATA	AGAATTGATT	ATTAACAGTT	AGCATTTTAT	TAATTACCTT	AACAATGATT
421	CAAGTTTAGT	TAAATGAGGT	TTAATTTGAA	AGGGAATAGC	GCCTCAATAT	AATGTAGGTA
481	GATTGTTCAT	ATTACGTAAT	TGAAAAATCA	AATTTAAATA	GATTGGGGCT	AAAAATTATG
541	AAATTTAAAG	CGATAGCAAA	AGCAAGTTTA	GCATTGGGAA	TGTTAGCAAC	AGGTGTAATA
601	ACGTCGAATA	TACAATCAGT	ACAAGCGAAA	ACAGAAGTTA	AACAACAAAG	TGAGGCTGAT
661	TTAAAACTTT	ATTATAATGG	ACCAAGTTTT	GAATATAAAA	AAGTAACTGG	ATATGGATTT
721	ATTGAAGGTA	AAGATAGATT	CATTGATTTT	ATATACAATG	GACAATATAA	TAAAATATCT
781	TTAGTTGGTT	CTGATAAAGA	TAAATATAAT	GAAGAAGTTA	ACCCAGATAT	AGATGTGTTT
841	GTCGTTAGAG	AAGGAAACGG	TAGACAAGCT	GATAATCATT	CGATTGGTGG	CGTAACAAAA
901	ACTAATAGAG	GAGTGTATTA	CGACTATATA	CACTCTCCAA	TCCTTGAAAT	TAAGAAAGGT
961	AATGAAGAAC	CACAAAATAG	TCTGTATCAA	ATTTATAAAG	AAAATATCTC	ATTAAAAGAA
1021	CTTGATTATA	GATTACGAGA	ACGTGCAATC	AAACAACACG	GATTGTATTC	AAATGGTCTT
1081	AAACAAGGTC	AAATTACAAT	TACTATGAAA	GATGGCAAAT	CACATACTAT	CGATTTAAGT
1141	CAAAAACTTG	AAAAAGAACG	TATGGGTGAT	TCTATCGACG	GCAGACAAAT	ACAAAAAATT
1201	CTAGTAGAAA	TGAAATAATA	CTTTCTAACG	ACAAAGCGCT	ATGTTGAATC	GTGCTTGTTA
1261	TGGAAATATA	TGGAAGTTAA	GCGACGTACT	GTTGCTTAGC	TTCTTTTTTG	AGGGCAAAGT
1321	TACAAAACTC	ACACAAACAG	TCGCAGCACG	CATTATCTTT	TACTTAACTA	GCTTAATCAT
1381	ATTTTATGAA	TAGTTAAAAA	AGGGTTAATG	TGAATATCAG	CATACAGCTC	CTATAATATG
1441	GTTGTATGAT	TCAATTTACG	TAATAAAACA	ATCTAATCTA	ATATATTGGA	GCATACAATT
1501	ATGAAAATGA	AATCAATTGC	AAAAGTAAGT	TTAGTGTTGG	GTATTTTAGC	TACAGGTGTA
1561	AATACTGTAA	CGGAACAACC	GGTGCATGCC	GAAAATAAAC	ATGTTCAAGT	AAGCCAAAAT
1621	AGTAAAAATT	TAAAAGCGTA	CTATACTCAA	CCTAGTGTTG	AATATAAAAA	TGTGACAGGT
1681	TATATCAGTA	GTATTCAACC	TAAACCAGGC	ACTAAATTTT	TGAATATGAT	AGAAGGTAAT
1741	ACAGTTAATA	ATCTAGCTTT	AGTTGGCAAA	GATAAGGAAC	ACTATCATAC	GGGTGTACAT
1801	CGCAACCTTG	ATATATTTTA	TGTTAATGAG	GATAAGAGAT	TTGAAGGTGC	AAAGTACTCG
1861	ATTGGTGGTA	TCACAAAAGC	AAGCGATAAA	GTTGTCGACC	AAGTAGCAGA	AGCAAGAGTC
1921	ATTAAAGAAG	ATCACACTGG	TGAATATGAT	TATGACTTTT	TCCCATTTAA	AATAGATAAA
1981	GAAGCAATGA	CATTAAAAGA	GGTTGATTTT	AAAATAAGAA	AACATCTTAT	TGATCATTAT
2041	GGTCTTTATG	GTGAAATGAG	TTCAGGAACA	GTTACTGTCC	AAATGAAATA	CTATGGCAAG
2101	TATACAATTG	AATTGGATAA	AAAGTTACAA	GAAGACCGAA	TGGCCGATAT	CGTCAAAGTC
2161	ATAGATATTG	ATAGGATTGA	AGTCAAAGTT	AAAAAAGCAT	AATGCTTAGA	CTGGTCGTCG
2221	TAATGAATTG	AAATTGCAAT	AGTGAGGTTA	AGTGATGATA	AAACGTTACT	TAACTTCTTT
2281	TTTATGTCTT	AAAATCATTT	CAAAGATACA	TAGTAACACC	ACATAAACCT	CGAAAGTACT
2341	CATTATTTTT	TGCTTAAATG	ACTTAATAAT	ATTTCAACAA	TTGTTAAACG	AGGGTTAATG
2401	TGAATAGACC	AATATGTCCT	CTATAATGAA	GTTGTATGAT	TCTAATTACG	TAAAGAACAA
2461	TCGAATAATT	ACGATTGGAG	CATACAACTA	TGAAAATAAG	AACAATTGCG	AAAGCGAGTA
2521	TAGCGTTAGG	GCTTGTAACA	ACAGGTGCAA	GTATAGTAAC	AACGCAATCG	GCCAATGCAG
2581	AAGTAGCATC	AGCACTTAAA	GCAGGACAGT	TAGCAAAGAT	AAACGTATCA	ACAAGCGCAA
2641	TCACAACGAC	AGCGCAAGCA	GTGAACGCAG	AACAAAATCA	TACGGCTAAT	CCTGAACAGG
2701	CGGCAAAGTC	TAACACAGAA	AATGTATCAA	CATCGCTTTC	AACTCAAACA	GAACAGACGC
2761	CAAAATCTAA	CATACAAAAA	GCAACACAAC	CAGCACCAAG	CGGAACAACT	CAGTCTTTAC
2821	CAAATGCACA	ACCGCAATCA	ACACAACCAA	CACCAAGTGT	AACAACACCG	CCTTCATCTA
2881	ATGTCGAAAC	ACCACAACCA	ACATCGCCAA	CCACAAAACA	AGCACAAAAG	GAAATAAACC
2941	CTAAATTTAA	AGGTTTAAGA	TCATATTATA	CGAAATCAAG	TTTAGAATTT	AAAAATGAGT
3001	TGGGTATAAT	TATCAAAAAA	TGGACAACAA	TAAGATTTAT	GAATATTGTT	CCAGATTATT
3061	TCATATATAA	AATAGCTTTA	GTTGGAAAAG	ATGATAAGAA	ATATGGTGAA	GGCGTGCATA
3121	GGCATGTCGA	TGTATTTATC	GTTTTAGAAC	AAAATAAATA	TGGCGTAGAC	AAATACTCGG
3181	TCGGTGGTAT	CACAAAAGCA	AATAGAAAGA	AAGTTGATTA	CAAAACTGGA	ATAAGTATTA
3241	CTAAAGAAGA	TAAAAAAGGT	ACAATCTCAC	ATGATGTTTC	AGAATACAAG	ATTACTAAAG
3301	AAGAGATTTC	CTTGAAAGAA	CTTGATTTTA	AATTGAGAAA	ACAACTCATT	GAACAACATA
3361	ATTTGTACGG	TAATATTGGT	TCAGGAACAA	TCGTTATTAA	AATGAAAAAT	GGTGGAAAGT

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3421  ACACGTTTGA ATTACACAAA AAATTGCAAC AACATCGCAT GGCAGATGTT ATTGATGGTA
3481  CAAATATTGA TAGAATTGAA GTGAATCTAA AATCATCGTG ATGGATACTA CATAGAACCG
3541  TTGAACGATG AAATGAGAAG TTAAGCGACA ATGACCTACA TCATTGCTTA GCTTCTTTTG
3601  TTTTGCGTAA TGATGTTAAG GGAAATTATT CACTTGTTTG TAAAAGTGAC ATCTCAATGT
3661  CTTGAAAATG ATGCAATGCC CAATGTGCAA GCGTTGAATC GCTTCGAAAC CATCTGTATT
3721  TAACGAAAAT TATGGATTAC TTAACGATGA TTCAAATATA GTTAAACATG GTTTAATGTG
3781  AATAGACCGA TACGTCTTCT ATAATGTAGT TGTATGATTC TAATTACGTA AAGAACAATC
3841  GAATATAATA GATTGGAGCA TACAACTATG AAAATGACAC AAATTGCGAA AACCAGTTTA
3901  GCACTATCAC TTTTAACAAC AGGTGCAAGT ATAGTAACAA CGCAATCGGC TAATGCAGAA
3961  GTAGCATCAG CACTTAAAAC AGAACAGGCA ATAAAATCTA AAATACAAAA AGTAACAACA
4021  TCGCCTTCAC CAAATGTACA ACCGCAATCG CCACAACCAA CACCAAGTGT AACAACTCCG
4081  CCTTCACCAA ATGTACAACC GCAATCGCCA CAACCAACAC CAAACCCAAC AACACCGCAT
4141  TCATCTAATG TCGAAACAAA ACAACCGCAA TCGCCAACCA CAAAACAAGC ACAAAAGGAA
4201  ATAAACCCTA AATATAAGGA TTTAAGAACA TATTATACGA AACCGAGTTT AGAATTCGAA
4261  AAGCAATTTG GCTTTATGCT GAAACCATGG ACGACAGTTA GGTTTATGAA TGTTATACCA
4321  GATTGGTTCA TTTATAAAAT AGCTTTAGTT GGAAAAGATG ATAAGAAATA TAAAGATGGG
4381  CCATACGATA ATATTGATGT ATTTATCGTT TTAGAGGACA ATAAATATCA ATTGAAAAAA
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4621  CAACATAATT TGTACGGTAA TATTGGTTCA GGAACAATTG TTATTAAAAC GAAAAACGGT
4681  GGGAAGTACA CGTTTGAATT GCATAAAAAA TTACAAGAAC ATCGCATGGC AGATGTCATA
4741  GATGGCACTA GTATCGAAAG AATTGAAGTG AATCTAAAAT CATCGTGATG GATACTGCAT
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4861  CTTTCGTGTT GCACAGTGGT ATAAGAAGAC GAATATTTGA TGTTGACCAC ACATAACATG
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4981  CATTTTTATT TAACGAACAT TATGGATTCC TTAATTTAAT TAACGATGAT TCAAATATAG
5041  TTAAACAAGG TTTAATATGA ATAGAGACAT ACGCCAACTA TAATAAAGCT GTATGATTCA
5101  ATAAACGTAA TCGAACAAAT CTAATAATTA CGATTGGAGC ATACAACTAT GAAGATGACA
5161  GCAATTGCGA AAGCCAGTTT AGCTCTAAGT ATTTTAGCGA CTGGGGTTAT AACATCAACG
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5401  ATACAAATTT TTGGTAAAGA TATAGAAAGG ATTAAAAAAC GTAAAAATCC AGGATTAGAT
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5521  ACTAAGAAAA ATCAAGGCGC TTACTATGAT TACTTAAGCG CACCTAGATT CGTTATTAAA
5581  AAAGAAGTAG GTGCAGGTGT TTCTGTGCAT GTTAAAAGAT ACTACATTTA TAAGGAAGAG
5641  ATTTCGCTGA AAGAACTTGA TTTTAAATTA CGACAGTATT TAATTCAAGA TTTTGATCTG
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5761  ACGTTTGAAC TCAATAAAAA GTTACAAACA AACCGAATGA GTGACGTCAT AGATGGCAGA
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5881  TATGGATAGT ATAGATGAGC TAGGCAGCAT AGGTTGCTTA GCTTCTTTTT TGTGTCGTTA
5941  CGATCGGAAA TGAAGTGGGT CGATGAAAGA TAATAACGAC AATAAAAACT GTGAAAATAG
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6121  TACTGTTAGG ATTCCATTAA TTAGCTTAAC ATTGGTTCAG GAATAGTTAA AAAGCGGTTA
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6241  ATTAATCACA TAAACATATA TTAAGTCAAA ATTTAAAAAT AGATTGGGAG AATAATACTA
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6421  ATGATATTAG AGATTTACAT CGATACTACT CATCAGAAAG TTTCGAATAT AGTAATGTTA
6481  GTGGTAAGGT TGAAAACTAC AATGGTTCTA ACGTTGTACG CTTTAACCCA AAAGATCAAA
6541  ATCACCAATT ATTCTTATTA GGAAAAGATA AAGAACAATA TAAAGAAGGT CTACAAGGCC
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7261  ACTTTATAAT AAAGGCAGAT GTTTCAAATT ACGTAATCAT AACAATCCAA TACATTAAGA
7321  TTGGAGCAAT AAATTATGAA ATTAACAGCA ATAGCTAAAG CAACATTAGC ATTAGGAATA
7381  TTAACAACAG GTGTGATGAC AGCAGAAAGT CAAACTGTAA ACGCGAAAGT AAAGTTGGAT
7441  GAAACACAAC GCAAATATTA TATAAATATG CTAAAAGATT ACTATTCTCA AGAAAGCTAT
7501  GAATCAACAA ACATTAGTGT TAAAAGTGAA GATTATTATG GGTCTAACGT TTTAAACTTT
7561  AACCAACGAA ATAAAAATTT CAAAGTATTT CTAATTGGCG ACGATAGAAA TAAATATAAA
7621  GAACTGACGC ATGGCCGTGA TGTCTTTGCA GTACCTGAAT TAATAGATAC TAAAGGCGGC
7681  ATATATAGCG TTGGCGGTAT AACAAAGAAA AATGTGAGAT CCGTGTTTGG CTATGTAAGT
7741  CATCCGGGAC TGCAAGTTAA AAAAGTTGAT CCTAAAGATG GCTTTTCGAT AAAAGAGTTG
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7801   TTCTTTATTC AAAAAGAAGA AGTATCATTG AAAGAACTTG ATTTTAAAAT CAGAAAAATG
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7921   ATGAAAGACG AAAAGAAACA TGAAATTGAT TTAAGTGAAA AATTAAGTTT TGATCGTATG
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8041   ATGATAGTAT AAAAAATTAA AAAGCGGCTT AACGATAAAA TGTGCATTGA CACCCGTACC
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8881   AGTTAGATTT TAAGTTGAGA AAGCATCTAA TTGAAAAATA CGGTCTTTAT AAAACACTCT
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9241   ACCATCAACA TCAAAATTCT CAACATCGCG ACACCACCAA ATGTTATAAT AAATCTATTA
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9661   AAGATTTCGA TATCGAACAT CTGGCGACGG CAATTCGTAA AGTTGAAACT TCAACACTAG
9721   GTGAAGAAAG TGAAAATGAC TTTATCGGAC TGTTCAGCGA TATGGACTTA AGTTCAACGC
9781   GTTTAGGTAA CAATGTCAAA GAACGTACTG CGTTAATTTC CAAAGTTATG GTTAACCTTG
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11881  AAGTTTAAAA CACATAGAAT GATTCATAAA TTTAAAATTA ATTCACAAGG ATTAACATCA
11941  GATACATGGA ACTTAAAATA TAAACAATTA AAAAATATAA ATATAGATAT ACCTGTATTG
12001  GAGGAACAAG AAAAGATAGG TGATTTCTTT AAAAAAATGG ATATATTGAT TAGTAAACAG
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12121  TAACTTTGAT AAACACATAG GTTGCATAAG AATAAAATTT GTGTAATTTA ACATAAAAGT
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12421 ACCGTTGCTC ATTATAATGA ATGAGGATTG TTCGTATTGC GTAATAGAAT AAATCAAATA
12481 GACTAAAAAT TGGGAGCATA GAATTATGAA ATTAAAAAAT ATTGCTAAAG CAAGTTTAGC
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12601 GCAAAGCAGA TTATCAGTTA CTTCAAACGA CACGCAAGAA TTAAAAAAAT ACTACAGTGG
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12961 AGCAGAAACT TATAGAATTA ATAAAGAAGA AATTTCATTA AAAGAATTAG ATTTCAAATT
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13261 GTTAGTATCT GTTGCAATTA CAATGTTATA TATCATGACA AACGGACAAG CAGAAGCATC
13321 AGAGGCTAAT GAGAAGCCAA GTACAAATCA AGAATCAAAA GTTGTTTCAC AGACTGAACA
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SEQ ID No. 106

***S. aureus* strain EMRSA 16(252) (SSL12-SSL14)**

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SEQ ID No. 107

***S aureus strain* MW2 (SSL 1 -11)**

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155461 ttcaaggtaa tccatcaact tggttctatc cattaggtga aaagaaagtt gaacgtaagg
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(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
6 October 2005 (06.10.2005)

PCT

(10) International Publication Number
WO 2005/092918 A3

(51) International Patent Classification:
C07K 14/31 (2006.01) *C07K 19/00* (2006.01)
A61K 39/085 (2006.01) *C12N 5/06* (2006.01)
A61K 48/00 (2006.01) *C12N 7/01* (2006.01)
C12N 15/62 (2006.01)

(21) International Application Number:
PCT/GB2005/001084

(22) International Filing Date: 22 March 2005 (22.03.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0406408.5 22 March 2004 (22.03.2004) GB
0412419.4 3 June 2004 (03.06.2004) GB

(71) Applicant (*for all designated States except US*): UNIVERSITY COLLEGE LONDON [GB/GB]; Gower Street, London WC1E 9BT (GB).

(72) Inventors; and
(75) Inventors/Applicants (*for US only*): CHAIN, Benjamin, Michael [GB/GB]; 46 Cleveland Street, London W1T 4JF (GB). NAIR, Sean, Paddy [GB/GB]; 256 Grays Inn Road, London, WC1X 8LD (GB).

(74) Agent: WOODS, Geoffrey, Corlett; J.A. Kemp & Co., 14 South Square, Gray's Inn, London WC1R 5JJ (GB).

(81) Designated States (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(88) Date of publication of the international search report:
27 April 2006

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2005/092918 A3

(54) Title: TARGETING POLYPEPTIDE

(57) Abstract: A targeting polypeptide is provided that may be used to target a chosen antigen to an antigen presenting cell. Complexes comprising such targeting polypeptide and antigen, nucleic acids and vectors encoding them, and cells comprising the nucleic acids and vectors may be used in methods of immunisation and enhance the immunogenicity of the antigen.

INTERNATIONAL SEARCH REPORT

ational Application No
/GB2005/001084

A. CLASSIFICATION OF SUBJECT MATTER
C07K14/31 A61K39/085 A61K48/00 C12N15/62 C07K19/00
C12N5/06 C12N7/01

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07K A61K C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2002/177551 A1 (DAVID S. TERMAN) 28 November 2002 (2002-11-28) page 2, paragraphs 14,19 page 3, paragraphs 21,22 page 8, paragraph 51-57 page 12, paragraph 89 - page 16, paragraph 132 page 21, paragraph 180 - paragraph 182; example 3	1-25

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 February 2006	09/03/2006

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Montero Lopez, B

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SHIMIZU MOTOMU ET AL: "A novel method for modification of tumor cells with bacterial superantigen with a heterobifunctional cross-linking agent in immunotherapy of cancer." MOLECULAR BIOTECHNOLOGY, vol. 25, no. 1, September 2003 (2003-09), pages 89-94, XP008052170 ISSN: 1073-6085 abstract page 89, right-hand column, paragraph 2 - page 90, right-hand column, paragraph 1	1-25
A	ERIC MURAILLE ET AL.: "T cell-dependent maturation of dendritic cells in response to bacterial superantigens" JOURNAL OF IMMUNOLOGY, vol. 168, 2002, pages 4352-4360, XP002368601 abstract page 4355, left-hand column, paragraph 2 - right-hand column, paragraph 1 page 4357, left-hand column, paragraph 2 - page 4358, right-hand column, paragraph 1	1-25
A	ALOUF J E ET AL: "Staphylococcal and streptococcal superantigens: molecular, biological and clinical aspects" INTERNATIONAL JOURNAL OF MEDICAL MICROBIOLOGY, URBAN UND FISCHER, DE, vol. 292, no. 7-8, 2003, pages 429-440, XP004959934 ISSN: 1438-4221 the whole document	1-25
A	WO 03/012111 A (LORANTIS LIMITED) 13 February 2003 (2003-02-13) page 2, last paragraph - page 4, line 15 page 8, line 14 - page 12, line 17 page 39, line 23 - page 40, line 10; example 1	1-25

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB2005/001084

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 17, as far as encompassing an in vivo method, and claim 24 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

ıational Application No
. ..:/GB2005/001084

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
US 2002177551	A1	28-11-2002	NONE		
WO 03012111	A	13-02-2003	EP	1419256 A2	19-05-2004
			JP	2005524381 T	18-08-2005
			US	2004213797 A1	28-10-2004